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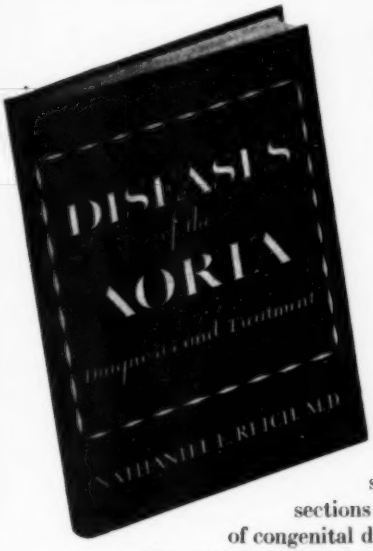

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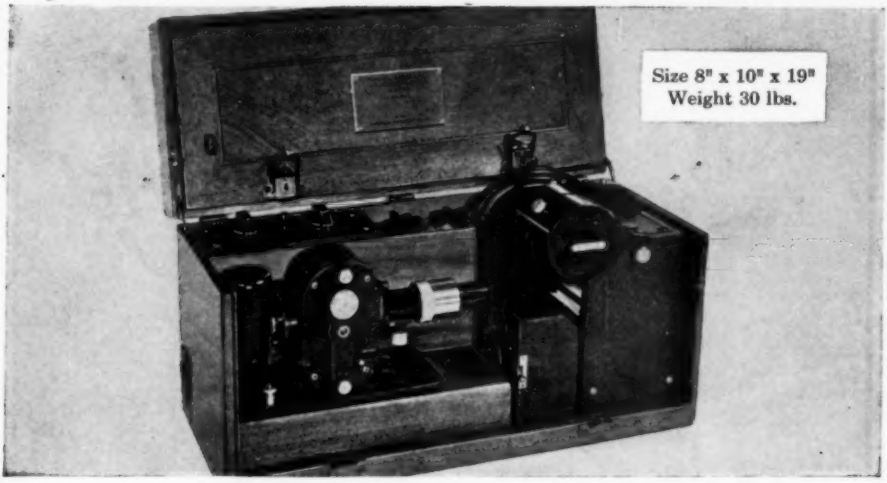

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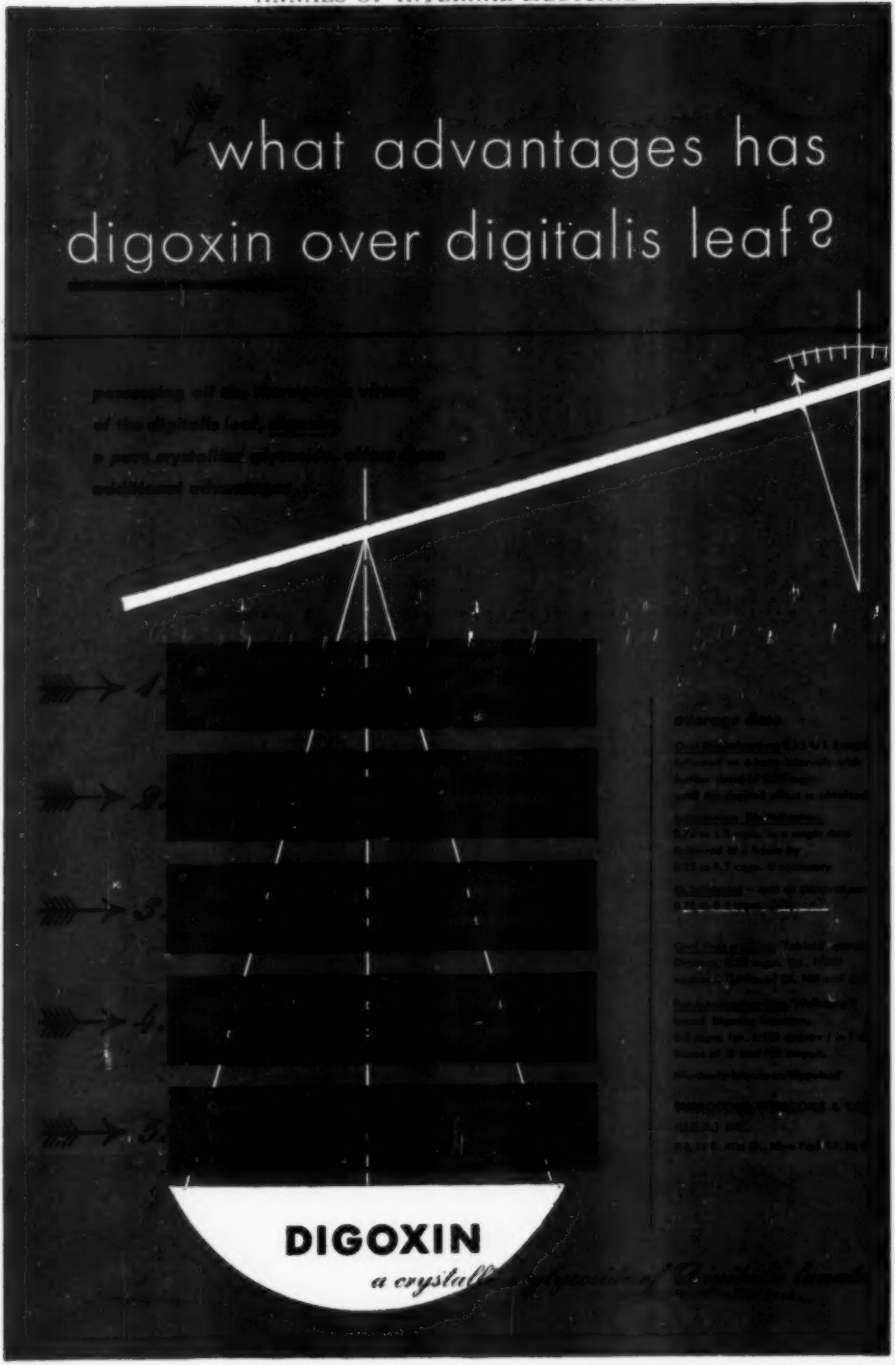
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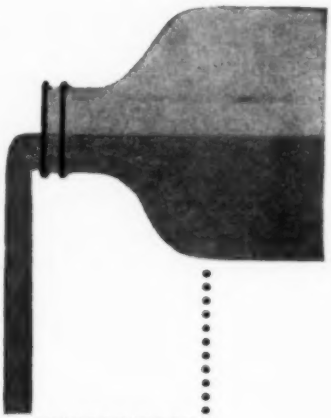

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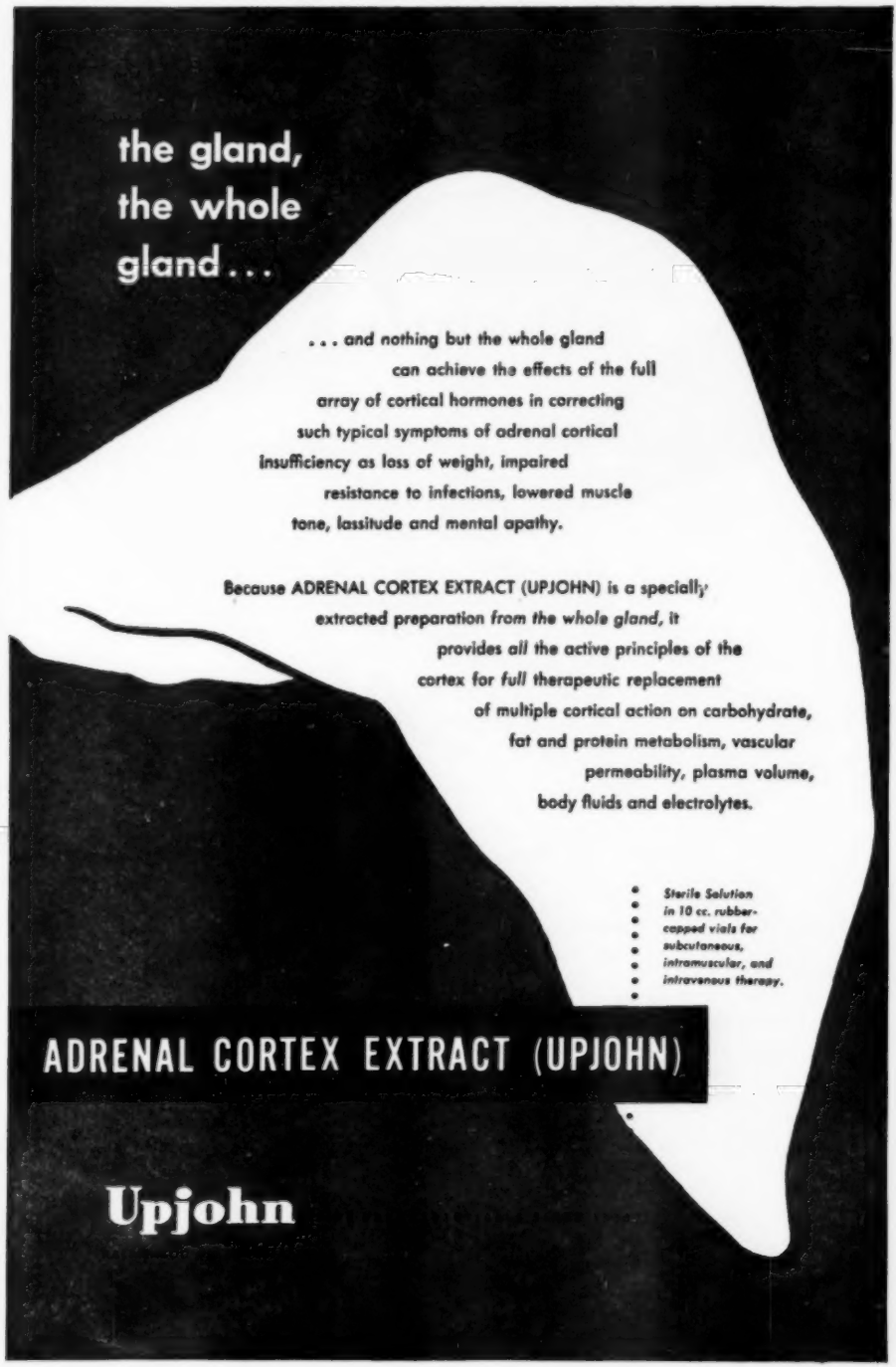
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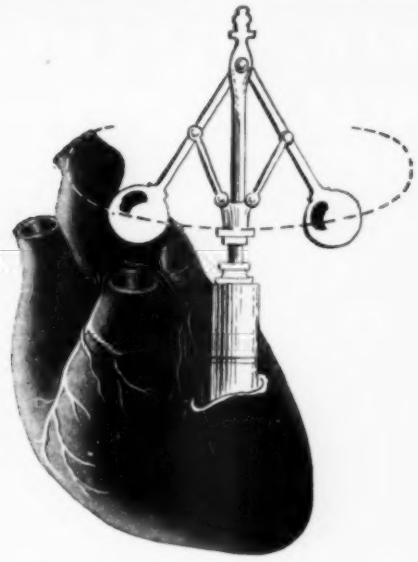

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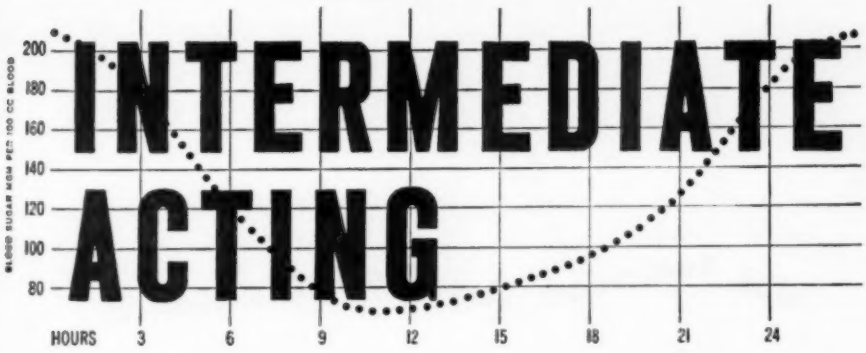

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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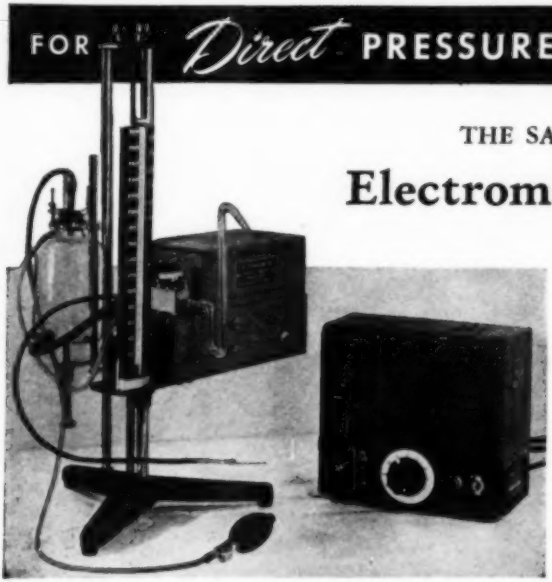

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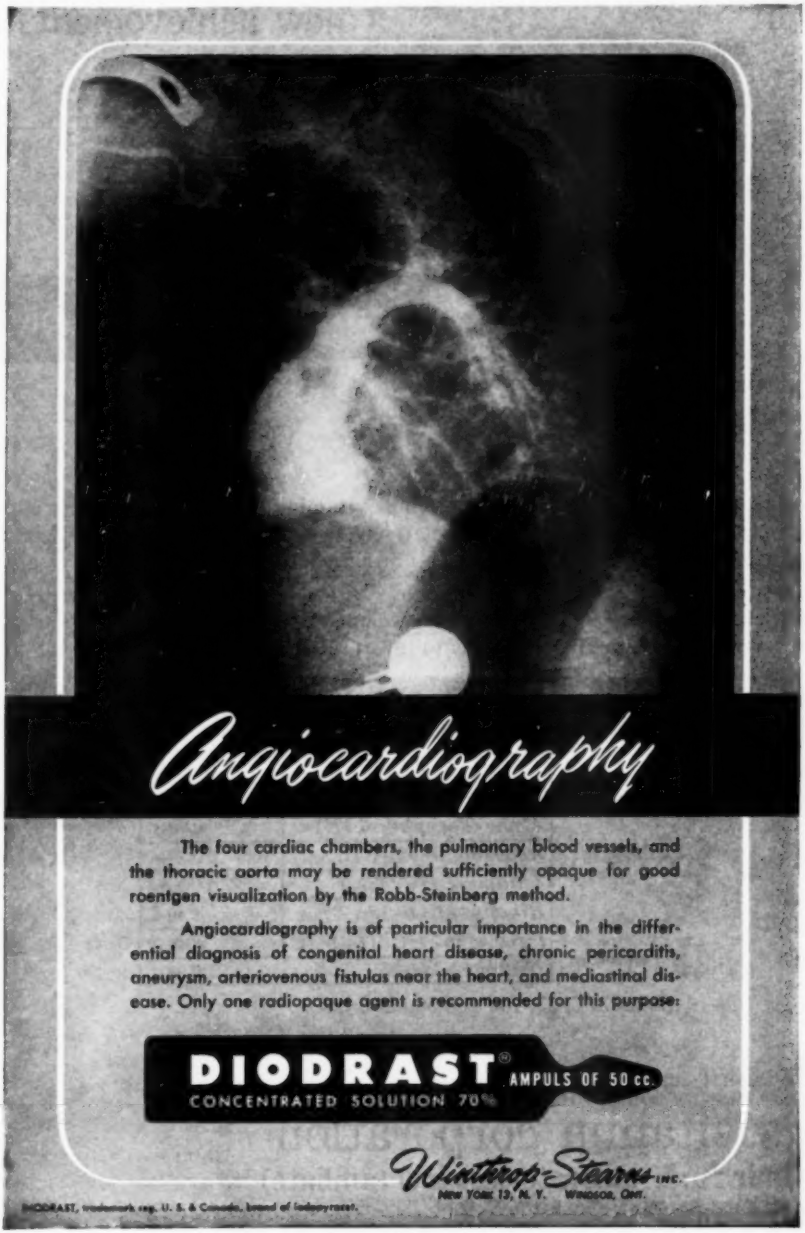
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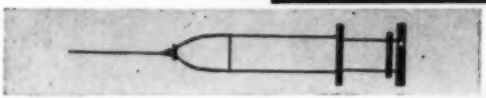

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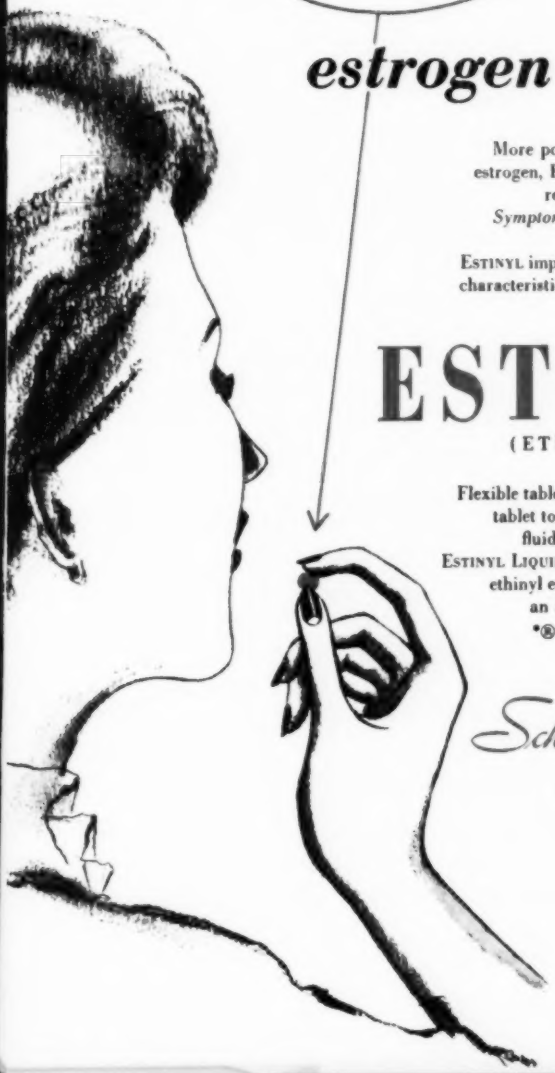

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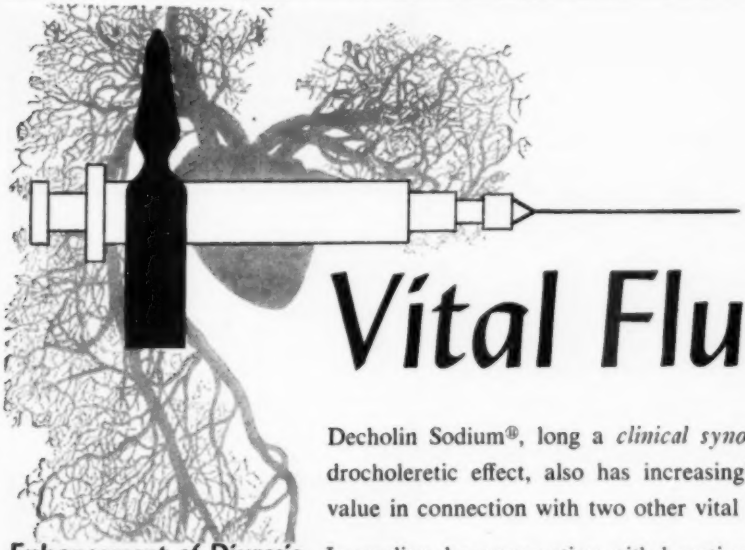

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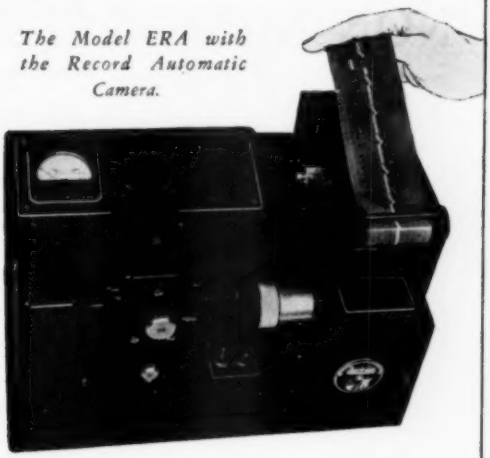

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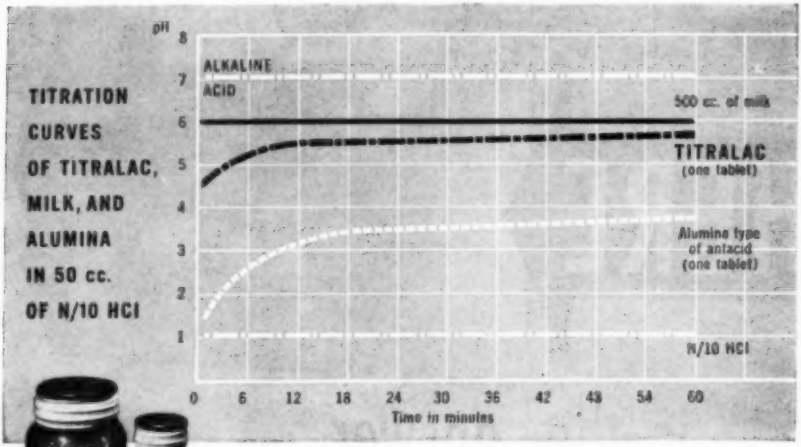

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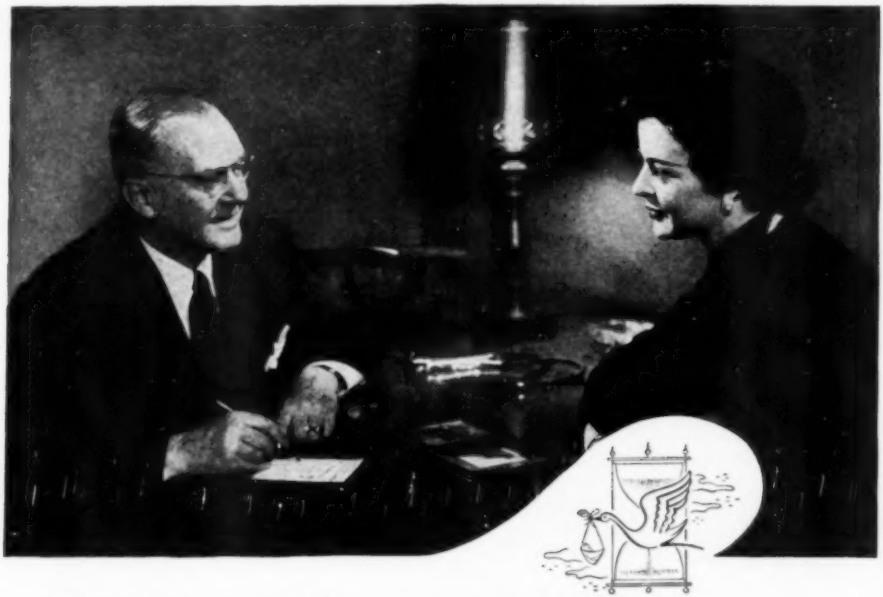

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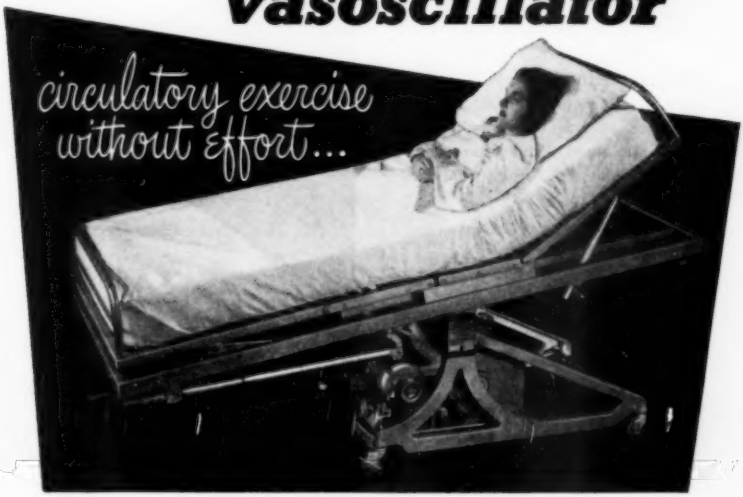

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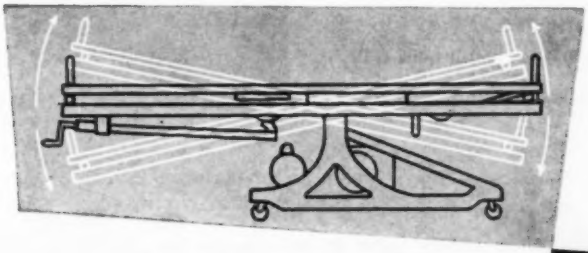

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ANNALS OF
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VOLUME 31 OCTOBER, 1949 NUMBER 4

THE USE OF BAL (BRITISH ANTI-LEWISITE) IN THE TREATMENT OF THE INJURIOUS EFFECTS OF ARSENIC, MERCURY AND OTHER METALLIC POISONS *

By WARFIELD T. LONGCOPE, F.A.C.P., and JOHN A. LUETSCHER, JR.,
Baltimore, Maryland

BAL (which stands for British Anti-Lewisite) or 2,3-dimercaptopropanol is a chemical found by Stocken and Thompson while working in Professor Peters' laboratory in Oxford, to be an effective antidote to Lewisite. This discovery made during the war represents the culmination of a long series of important investigations carried on for many years by several investigators, but especially by Professor Peters and his associates in Oxford.

For some time it had been known that the injurious effect of arsenic depends upon its attachment to the sulfhydryl groups of cellular proteins thus interfering with the function of essential enzymes which require the free sulfhydryl grouping for their action. Previous efforts had been made, particularly by Voegtlin [1] to counteract the injurious effects of arsenical intoxication with sulfhydryl containing chemicals such as cysteine and glutathione but these proved only partially effective. The secret of the success obtained by Stocken and Thompson [2, 3] lay in the fact that BAL which is a dithiol formed a compound with arsenic which was non-toxic and much more stable than the compounds resulting from the action of the mono-thiols.

There is not time, nor have I the special knowledge even to outline the brilliant series of investigations by Professor Peters and his associates and others which finally led to the discovery of BAL, but those interested in this phase of the subject can obtain much information from the reviews by Peters and Stocken,[4] and by Waters and Stock [5] as well as by a recent lecture of Professor Peters [6] in the Proceedings of the Royal Society of Medi-

* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.
From the Medical Clinic of The Johns Hopkins University and Hospital.

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cine for November 1948. A consideration of this entire subject will appear shortly in Advances in Internal Medicine.[7]

Suffice it to say that the implications which these experiments have for investigations in enzyme chemistry and allied biological processes probably far outweigh any immediate practical significance they may have for clinical medicine. But, in as much as they do bear on certain therapeutic problems it will be my function to consider this aspect of the subject.

My interest in this matter came through work during the war under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins Hospital, and in coöperation with the Medical Laboratories at Edgewood Arsenal. Under this contract Dr. Luetscher and I were asked to study and treat cases of accidental injury caused by contact with poisonous war gases which might occur at Edgewood Arsenal.

We were fortunate at this time in having the information from the British workers, and knew that Peters and his associates had found that BAL would prevent blistering of the skin by Lewisite or indeed would bring about complete reversion to normal when applied to the skin even 15 to 30 minutes after Lewisite, at a time when reddening had already occurred. BAL would also combat systemic poisoning of rats by other arsenicals such as mapharside and neoarsphenamine, while Eagle[8,9] in this country had found that trypanosomes immobilized by arsenicals, and rabbits in desperate condition after receiving a lethal dose of mapharsen could be revivified by BAL. When therefore some cases of arsenical dermatitis due to contact with adamsite or diphenylamine chlorarsine, which had resisted treatment, were sent to us from Edgewood we decided to try the effect of applications of a salve containing 5 per cent and 10 per cent BAL to the eruption. The results were so satisfactory that we thought it desirable to extend this form of treatment to cases of dermatitis complicating the arsenical therapy of syphilis. Similar observations were being carried out at the same time by Carleton, Peters, Stocken, Thompson and Williams[11,12] in England and by Eagle and Magnuson[10] in this country.

Before reporting further on this work, it would be well to refer to the materials and dosage employed and to the toxic effects of over dosage. BAL was employed at first in a 5 per cent or 10 per cent ointment, but as soon as Eagle had devised a preparation that could be used for intramuscular injection this was substituted for the ointment. This preparation is commercially available in sealed capsules and consists of 5 per cent or 10 per cent BAL in 20 per cent benzylbenzoate in peanut oil. From the work of Sulzberger[13] and his associates, of Modell[14] and his associates and of Eagle and Magnuson[10] it has been determined that a single intramuscular injection of 3.0 mg. per kilo of the 10 per cent solution of BAL very rarely produces unpleasant symptoms in the normal individual. As BAL is rapidly excreted, a dose of this size may be administered with impunity every four hours. When a dose of 5 mg. per kilo is used, in two-thirds of the subjects,

symptoms of intoxication appeared within a few minutes, reached their height within 10 to 30 minutes and then subsided. Tye and Siegel[14a] state that the unpleasant symptoms caused by BAL were relieved in one patient by the administration of 0.6 c.c. of 1–1,000 solution of epinephrine hydrochloride intramuscularly and were prevented in this patient and in one other by an oral dose of 25 mg. or 50 mg. of ephedrine given one-half hour before the injection of BAL.

The symptoms are as follows:

TABLE I

Symptoms of Poisoning by BAL

1. Nausea and vomiting.
2. Headache.
3. Burning sensation of lips, mouth, etc.
4. Feeling of constriction of throat, chest and hands.
5. Conjunctivitis, tearing and salivation.
6. Tingling of hands.
7. Burning sensation of penis.
8. Sweating of forehead and hands.
9. Abdominal pain.
10. Tremors and shakiness.
11. Lower back pain.
12. Elevation of blood pressure.

Our experience[15] in treating post arsphenamine dermatitis by BAL was somewhat limited for we had only 15 cases, but the results were similar to those of Eagle and Magnuson[10] who reported 88 cases and of Carleton, Peters[11, 12] etc. who have now recorded their results in a total of 74 cases.

In general it may be said that on the schedule of dosage employed the results have been very satisfactory in the majority of cases, with dramatic improvement in many instances. Often within 24 to 48 hours after the intramuscular injections are started, even in severe cases, the erythema, edema and itching of the skin subside, while the weeping vesiculitis becomes dryer. In the early stages scaling may set in, and in the more advanced cases exfoliation may actually increase. Occasionally progressive recovery takes place with surprising rapidity, but usually even when the course is favorable it is several days before healing of the skin is complete. Nevertheless five of our patients were completely well within 12 days. Eagle states that of 51 patients suffering from a severe form of exfoliative dermatitis, 40 showed improvement five days after BAL therapy was instituted and the majority had "recovered" by the fifteenth day. Carleton and Peters in their recent paper[12] state that the response to treatment was beneficial in 70 per cent of their cases, the mean duration of the dermatitis being 21.5 days in contrast to a control series not treated by BAL in which it was 62.5 days. In a control series collected by us the average duration of the dermatitis was 67.3 days.

The amount of arsenic employed in the treatment of syphilis, the occurrence of dermatitis in hypersensitive patients after small doses of the arsenical and the presence of secondary infection of the skin all seem to have

some bearing on the rate of recovery. Certainly the amount of BAL employed as well as the duration of treatment are important factors for it frequently happens that relapses occur when the course of injections is not sufficiently protracted.

Perhaps one of the best evidences that arsenic is actually extracted from the tissues by BAL is the increased urinary excretion of arsenic following the administration of BAL. With the aid of Dr. Eagle [10] and his staff this could be demonstrated in eight of our patients suffering from arsenical dermatitis.

Since the publication of these early papers, evidence is slowly accumulating to show that BAL is effective in several forms of arsenical intoxication. Eagle [10] found it particularly efficacious in hemorrhagic encephalitis (five cases) and possibly of value in blood dyscrasias (15 cases) while Holley [17] has reported the treatment with BAL in 12 cases of agranulocytosis without a death. The immediate use of BAL in cases of accidental overdosage of antisyphilitic arsenical poisoning has been attended with phenomenal success.[10, 18] Others [18a] have reported good results in the treatment of post arsphenamine thrombopenic purpura and in optic neuritis [18b] following the use of trypanarsamide.

The promising results obtained by the use of BAL in arsenical dermatitis led us to test its value in combating intoxication by other heavy metals.

Bichloride of mercury has been used quite frequently in Baltimore for the purpose of committing suicide, and we decided to try the effect of BAL in the treatment of such patients. At this time we were familiar with the experimental investigations of Gilman and his associates [19] at Edgewood Arsenal, which showed clearly that rabbits could be saved from lethal intravenous doses of mercury when BAL was administered within 15 to 30 minutes. If mercury bichloride was given to dogs by mouth, BAL was often effective when administered as long as three hours later. These observations stimulated us at that time to collect as many cases of bichloride poisoning as possible.[20] Thompson and Whittaker [20a] found that BAL will protect the pyruvate oxidase system of brain from the toxic effects of mercury while Stocken [20b] showed conclusively that BAL injected intramuscularly five minutes after a fatal dose of mercury given intraperitoneally protected rats. When mercury was given by mouth, 75 per cent to 100 per cent of rats could be saved if BAL was injected even after 30 minutes followed one and one-half hours later by an oral dose of BAL.

Since then we have treated many more patients so that it is now possible to report on the effect of BAL therapy observed in a total of 61 patients suffering from acute poisoning by mercury bichloride. The results seem to demonstrate conclusively that BAL is an effective antidote to bichloride of mercury when treatment can be instituted within the first few hours after poisoning has occurred.

The amounts of mercury bichloride which the patients swallowed varied from 0.5 gram to 20 grams, and 41 of the 61 patients had swallowed 1.0 gram or more (table 2). Many of these patients were desperately ill when

admitted to the hospital. A few were in collapse, several were vomiting blood and suffering from abdominal pain and bloody diarrhea. A few showed superficial ulceration of the gums and fauces or bluish black discoloration of the tongue. Serious uremia developed in four patients, two of whom recovered. Two of the 61 patients died, one being the first patient treated with inadequate amounts of BAL, 13 hours after the ingestion of at least 1 gram of bichloride, the other was a woman treated five and one-half hours after swallowing at least 2 grams of bichloride. Both died in uremia.

Of the 59 patients who recovered, improvement occurred in all but two with astonishing rapidity. Nausea, vomiting, diarrhea and abdominal pain were relieved within 24 to 48 hours, and even the most severely poisoned patients were symptomatically well within three to four days. There were no complications or residua such as persistent diarrhea, anemia, loss of weight or ulceration of the buccal mucous membrane. The two patients in whom convalescence was prolonged had persistent renal insufficiency, complicated in one by pneumonia.

TABLE II

$HgCl_2$ Poisoning
61 Cases treated with BAL

Grams $HgCl_2$ Dose	Patients	Recovery	Death
0.5	20	20	0
1.0	18	17	1
1.5	12	12	0
2.0+	11	10	1
	61	59	2

It soon became evident that there were at least two important factors that might determine the outcome in these patients. One was the period intervening between the ingestion of bichloride and the start of treatment by BAL and the other, the amount of BAL administered and the duration of treatment.

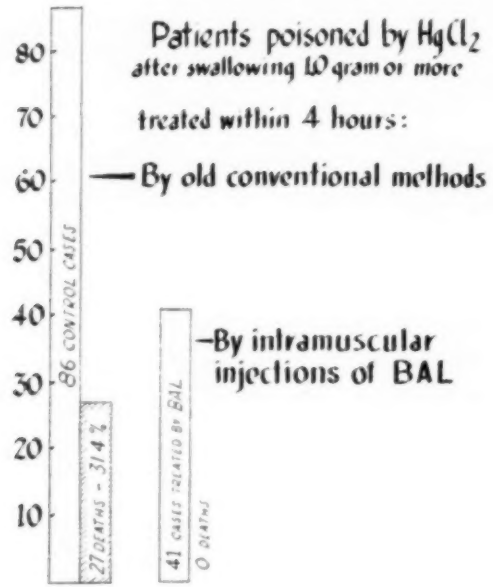
Prompt institution of treatment by BAL is of paramount importance. This becomes evident when the outcome is compared in 38 patients who had taken from 1 gram to 20 grams of bichloride and were treated with BAL within four hours to a similar control group of 86 patients not treated with BAL but by the older conventional methods. There were no deaths in the 38 receiving BAL and 27 deaths in the 86 without BAL. A dose of 3 grams or more of bichloride killed eight of nine patients not treated by BAL while after prompt treatment of BAL all of four patients survived 3 to 20 grams of the poison.

One of the deaths in the series treated with BAL occurred in a woman who had swallowed at least 1 gram of bichloride 13 hours before admission, and had severed the arteries in both wrists. She also received insufficient amounts of BAL. The other death was in a woman who had swallowed 2

grams of bichloride five and one-half hours before admission, and who received adequate amounts of BAL.

It is essential that sufficient amounts of BAL should be administered at the earliest possible moment. The first dose of BAL was 300 mg., which in many patients amounted to 5 mg. per kilo. This was followed within two to four hours by 150 mg. which in severe cases was repeated at four hour intervals for 24 to 36 hours. In consequence many patients received as much as 600 mg. to 750 mg. of BAL during the first 12 hours. The dose was reduced as rapidly as the symptoms abated but was frequently continued in amounts of 150 to 300 mg. a day for several days. This seemed

TABLE III



necessary when large doses of mercury bichloride had been ingested. Mercury appeared in the stools of one patient who had swallowed 3 grams of bichloride for as long as 15 days, and signs of renal insufficiency increased when treatment by BAL was prematurely stopped. No serious toxic effects from the use of BAL were observed in any of these patients, in spite of the fact that the individual doses as well as the total amounts were sometimes larger than those usually advised; for 18 patients received a total amount of 1.5 grams to 3.0 grams during the course of their treatment. A few patients complained of transient tingling of the tongue, the lips or the ex-

tremities following a single injection. One patient complained of flushing of the face, fullness in the head, sweating, shooting pains in the arms, legs and burning in the epigastrium after a dose of 300 mg. of BAL. Two women were observed to have cardiac irregularities due to extrasystoles following single doses of 150 mg. of BAL. A great many patients showed a moderate elevation of blood pressure within the first 24 or 48 hours after admission, but it is questionable as to whether this was due to BAL.

The tolerance that these patients appeared to show for BAL was interpreted as being due to the fact that the large quantities of mercury present in the body combined with all or most of the BAL which was injected. As the complex is rapidly eliminated, and devoid of toxic properties, both mercury and BAL were rendered inert.

Adjuvant treatments have been employed. Practically all patients were subjected to gastric lavage with sodium formaldehyde sulfoxylate on admission and were given large quantities of fluid during their course in the hospital. Blood transfusions were given to a few patients who were admitted in shock.

It has recently been shown by Sussman and Schlack [21] that BAL annuls completely the diuretic effect of mercuhydrin, and by Long and Farah [22] that it combats the acute toxicity of salyrgan in animals.

Efforts have been made to extend the use of BAL to control the poisonous effects of other metals. Favorable results have been reported in the treatment of several of the untoward complications of gold therapy. These include dermatitis, stomatitis, thrombopenia, purpura and granulocytopenia.[23, 24, 25, 26, 27, 28]

There is some experimental evidence to indicate that BAL may have a beneficial effect in poisoning by antimony (Braun, Lusky and Calvery [29]; Gammill, Southam, etc.[30]; Eagle, Germuth, etc.[31]).[29a]

Lead is a common form of metallic poisoning and it was hoped that BAL might prove to be a valuable remedy for this form of intoxication. Experimental investigations have, however, shown as was observed first by Braun, Lusky and Calvery [29] that exactly the opposite result takes place. For the administration of BAL to animals acutely poisoned by lead, actually enhances its toxic effect. This may be due, according to Germuth and Eagle [32] in part at least to the fact that the BAL-lead complex proved in their experiments to be almost as toxic to rabbits as lead itself. They have shown, nevertheless that a single dose of BAL injected into rabbits, which had previously received lead acetate, did increase the urinary excretion of lead 11 to 40 fold within two hours. Ryder, Cholak and Kehoe [33] administered BAL to men suffering from lead poisoning and following single doses noted an increase in the urinary excretion of lead which reached its peak within one to two hours. The injections of BAL did not have any beneficial effect upon the symptoms of lead poisoning in these individuals. We have had the same experience in one patient suffering from anemia and intestinal colic due to lead poisoning who, after each of two courses of BAL, excreted large

amounts of lead in the urine but who showed no coincidental improvement of symptoms. At the present time there seems to be no experimental basis for the therapeutic use of BAL in lead poisoning in human beings. Telfer [33a] on the other hand reports a patient with acute lead poisoning, who recovered rapidly following two courses of BAL. During the first course there was marked increase in the urinary excretion of lead with some exacerbation of symptoms; during the second course, a pronounced increase in the urinary excretion of lead occurred again, without, however, any return of symptoms.

The results are somewhat analogous to those that have been reported by Gilman, Philips [34] and their associates in experimental cadmium poison. The complexes formed by the combination of BAL and cadmium "in vitro" are readily dissociable and are as toxic as cadmium itself. Rabbits given a prophylactic dose of BAL and then injected with lethal or sub-lethal amounts of cadmium, were protected against the acute toxic effect of cadmium, which otherwise would have been fatal within 24 hours, but died after several days in renal insufficiency. They offered the suggestion, as an explanation for the unexpected result, that the dissociation of the BAL-cadmium complex took place in the kidney, and thus the cells of this organ were subjected to the action of cadmium in high concentration.

There seems to be no adequate explanation as to why BAL given immediately prior to an injection of alloxan in rats prevents completely the appearance of diabetes. According to Lazarow [35] and to Chesler,[36] BAL acts only as a protective measure, for if it is injected even five minutes after alloxan is administered, diabetes appears as usual.

Perhaps the most recent use to which BAL has been applied is in the treatment of polyneuritis. Within the last few months, Furmanski [37] has reported four patients with infectious and metabolic neuropathies, who did not respond to treatment with vitamins or crude liver extract, but three of whom made a rapid recovery and one of whom showed improvement after injections of BAL had been instituted.

In addition, therefore, to the extensive experimental investigations that have been made concerning the action of BAL in its relation to the injurious effects that several heavy metals have upon the cells of the body, and to the observations, that are still limited upon the therapeutic value of BAL in these conditions, it is very likely that further research may broaden our knowledge of the properties of this dithiol.

However this may be, it seems justifiable to conclude that at least three significant results have emerged from the many valuable studies on the action of BAL. First, the bearing which the fundamental concept of the action of BAL has had and will have on experimental investigations in biochemistry. Second, its practical value which seems to be considerable in the treatment of arsenical dermatitis as well as other forms of arsenical intoxication. Third, its remarkable curative property, when used early and in sufficient amounts in poisoning by mercury and possibly by gold.

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THE DIVERSITY OF GOUTY ARTHRITIS AND ITS COMPLICATIONS *

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THE clinical manifestations of gouty arthritis as it is usually seen are well documented and are readily recognized, be they associated with the acute involvement of the joints or the chronic changes. Less well appreciated are the vagaries of metabolic gout which include the unusual aspects of gouty arthritis in addition to the definitive complications which may embrace non-articular structures of the body. Although the malady is a chronic one interspersed with acute exacerbations in all afflicted persons, it may be associated with a great diversity of clinical manifestations. In some patients irreparable joint involvement may be so extensive, especially of the hands and the feet, as to lead to rheumatic invalidism. Less than 5 per cent of the gouty patients seen by us would be so classified.[1] When the disease progresses to this degree the patient is truly an invalid and may be as crippled as a patient with advanced rheumatoid arthritis. Furthermore, rheumatoid arthritis may be associated with gout in an occasional patient. An illustration of crippling gouty arthritis, as well as one with gout plus rheumatoid arthritis, will be discussed below. On the other hand, one encounters occasionally a patient with gouty arthritis who has lived three score and ten years but with no gross irreparable damage to the joints which is specifically attributable to gout. Such patients have acute attacks of joint disease, they respond well to colchicine, but the metabolic affliction is little more than a nuisance at any time and produces no greater injury to the cartilage of the joints than to the cartilage of the ear.

Although involvement of the joints is the identifying characteristic of the malady, during acute episodes as well as after the development of chronic changes, pathologic embarrassment of the kidney and complications associated therewith may produce critical clinical findings and in some patients may lead to death from renal insufficiency. Renal failure is the most important cause of death of gouty patients, irrespective of age, and the only important cause of death prematurely. Chronic renal impairment may go hand in hand with advanced joint disease or it may completely overshadow what appears clinically to be relatively minimal joint involvement. Case

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illustrations of each variation will be presented. Finally, in order that the "typical" case of gouty arthritis be not slighted one such case is included.

The several case illustrations will not be presented with complete clinical and laboratory findings. Pertinent data to emphasize certain points only will be given. In each instance the diagnosis of gout has been established by all or almost all of the following criteria: (1) positive family history for gout, (2) typical acute attacks of joint distress, (3) response to full doses of

FIG. 1. Roentgen-ray of left foot, patient 1, taken at the age of 21. It is interpreted as a normal foot.

colchicine, (4) evidence of osseous tophi by roentgen-ray examination, (5) elevation of serum uric acid above 6.0 mg./100 c.c., (6) subcutaneous tophi with recovery of sodium urate crystals and (7) renal disturbance.

Case 1. M. F. is an example of a relatively young man who has been observed intermittently for more than 15 years. He became a cripple from gouty arthritis during a relatively short period of time, less than five years. He is now 37 years old. He was seen first in 1933 at the age of 21 and offered to participate in metabolic studies pursued by the writer in coöperation with Drs. Walter Bauer [2] and Bernard M. Jacobson.[3] Metabolic data from these studies have appeared in the medical literature from time to time in the intervening years. There is no one in the author's series who has been a more coöperative experimental subject and for whom so little has been accomplished to

delay progression of irreparable damage. The patient is not a physician but his understanding of the disease would command the respect of many members of the profession. The family history is negative for gout but his mother had an elevated concentration of serum uric acid. She died in 1944 of myocardial infarction.

At the age of six, the patient had trouble with his left hip, a diagnosis of tuberculosis of this joint was made and the leg was immobilized for eight months. In retrospect it is believed that the joint trouble most likely was gout and not an infectious process. At least there was no evidence to suggest tuberculosis except the clinical impression, either before or after this event. At the age of 12 there was inflammation of various joints which persisted several days. During the next eight years he noted a

FIG. 2. Roentgen-ray of left foot, patient 1, taken at the age of 25. Many osseous tophi are seen. There is no structural deformity and minimal soft tissue changes.

decreasing interval between acute attacks and by the time he was 21 he had several acute attacks per year. Following subsidence of the acute joints with colchicine therapy, his physical examination was quite negative. Between attacks there was no evidence of joint disease, no limitation of motion, no subcutaneous tophi and no changes in the joints by roentgen-ray (figure 1). He was not long to be spared the chronic stigmata of the disease, however, and within the next 18 months urate tophi appeared on the hands and ears. The first roentgen-ray changes noted in the hands and feet were observed at the age of 23. There were discrete osseous tophi which did not appear to involve grossly the articular spaces. He had frequent attacks of acute arthritis which responded well to colchicine but progression of this disease, clinically and by

roentgen-ray, was more rapid than that which has been observed in any other patient. At the age of 25 there were innumerable osseous tophi evident (figure 2). Five years after the first osseous tophi were seen, the bones of the hands and feet were riddled with disease, advanced gouty changes were evident and in some bones expansion of the cortex from urate deposits was demonstrated readily (figure 3). Massive accumulations of sodium urate appeared about many of the peripheral joints. Discharging sinuses made it difficult to carry out foot hygiene and amputation of the toes in several stages became necessary in his early 30's. At 37 the lower leg was amputated because

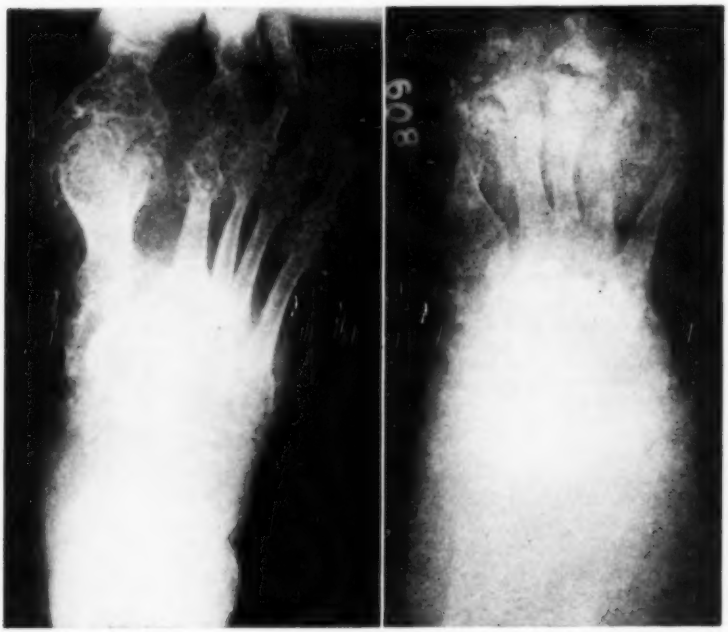

FIG. 3. (Left) Roentgen-ray of left foot, patient 1, taken at the age of 28. The osseous tophi have expanded the bones and joints, the cortex is a mere shell and soft tissue swelling is extensive.

FIG. 4. (Right) Roentgen-ray of amputated left leg, patient 1, taken at the age of 37. All of the toes have been amputated. The massive urate deposits are evident.

it was functionless and devitalized. A roentgenogram taken at the time of amputation (figure 4) showed a mere shell of bony structure with all toes removed. A cross section of the specimen (figure 5) illustrates the extent of deposits of sodium urate. The patient has been confined to bed for several years. Hardly a joint in his body has escaped acute arthritis and infiltration with urates.

Comment. This patient is believed to be the youngest in the series to develop acute gouty arthritis i.e., at the age of six. He is the youngest, also, who is a cripple from rheumatic gout. The duration of the disease, 30 years,

is no longer than frequently seen. The number of days per year, however, that he has suffered from acute arthritis is probably the maximum in our experience. This case lends support to the hypothesis that the number of days per year in which the patient is acutely afflicted, influences markedly the degree of permanent involvement. A mild case of gout over a period of years usually means an occasional attack only and little or no serious joint involvement. Per contra, a severe case probably implies many attacks per year and eventually extensive joint involvement.

Case 2. H. K., a female with advanced gouty arthritis, had her first joint trouble at the age of 14. During the next 30 years she had one or more attacks of mild to moderate acute gout annually. The family history was positive for gout. Her father had a mild form of the disease. His serum uric acid was 7.7 mg. per cent. At the age

FIG. 5. Cross section of amputated leg, patient 1. Urate deposits have replaced most of the normal structures of the foot.

of 34 she had a bilateral oophorectomy and a hysterectomy. When she was seen first by us at the age of 44 she had extensive subcutaneous deposits of sodium urate and moderate involvement of the bones and joints by roentgen-ray (figure 6). More disturbing from a clinical standpoint was the renal involvement. The urine showed albumin in all samples, the maximum specific gravity of the urine following abstinence from fluid for 12 hours was 1.013 and the excretion of phenolsulphonphthalein dye, 1 c.c. injected intravenously, was less than 8 per cent in the first 15 minutes. The serum uric acid was 8.2 mg./100 c.c. The non-protein nitrogen was 38 mg./100 c.c. During the next five years she developed progressive nitrogen retention and a gradually increasing concentration of uric acid in the serum. At several examinations it was greater than 10 mg. The joint involvement progressed also but her incapacity late in the disease was largely related to renal insufficiency. She died at the age of 49 in uremia.

Comment. This is an illustration of a patient with gout, who died prematurely from renal insufficiency. Although her gouty arthritis was extensive she had been able to support herself at work until a few months before death. Many of her joints had limitation of function but she was invalided primarily because of renal disease. The nature of the renal involvement was no more established than it is in many patients who have this serious complication of gout. She had a urinary tract infection which produced symptoms from time to time but pyelonephritis was not believed to account primarily for the kidney involvement. The pathology of the kidney in gouty patients who die in renal failure has not been specific in any of the cases studied. Changes consistent with nephrosclerosis, chronic glomerular nephritis, urate nephritis or pyelonephritis may be interspersed throughout the renal parenchyma. The term mixed nephritis, an admittedly unsatisfactory designation, has been applied in some instances.

After the detection of moderate renal impairment, the joint disease appeared to progress rather rapidly. It might be argued that the impaired excretion of nitrogenous products, including uric acid, hastened the joint disease. Undoubtedly this is a valid assumption. On the other hand, subcutaneous and osseous tophi may appear without extensive renal impairment as noted in patient 1 and lethal renal disease may be associated with minimal joint trouble as is noted in patient 3.

An additional reason for including this patient was the appearance of unequivocal gout in a female before the menopause, possibly before or at the time that her menses began. This is contrary to the teaching of Hippocrates who affirmed that: "A woman does not take the gout, unless her menses be stopped." The positive family history is observed in a majority of patients with gout. There appears to be no correlation between severity of the disease in the parent and in the child. Mild cases have been observed in children of severely afflicted fathers and vice versa.

Case 3. C. C., a white male, was seen first at the age of 39, complaining of recurring attacks of acute arthritis. It was considered significant that albuminuria was detected at the age of 20 while he was in the service in 1917 in France. Although he was hospitalized but for a few days and does not recall that a diagnosis of acute nephritis was mentioned to him, he received partial disability on separation because of renal disease. There were no renal symptoms and no subsequent study made of the status of his kidneys until he was 39. At this age he stated that he had had acute attacks of arthritis which involved toes, ankles, knees, hands and elbows during the preceding 10 years. The acute episodes appeared every other year for the first six years, and approximately once a year thereafter. A tophus on the ear was noted at the age of 33 A duodenal ulcer was diagnosed by roentgen-ray six months before he was first seer in this clinic. At this examination the blood pressure was 148 mm. Hg systolic and 102 mm. diastolic; the physical examination was quite negative otherwise except for acute gout in the right foot. The roentgenograms of the hands, feet and knees were negative except for one area of diminished density at the base of the first phalanx of the right great toe (figure 7). The serum uric acid was 8.9 mg. per cent and serum non-protein nitrogen was 83 mg. Albumin was present in all urine samples. The excretion of phenolsulphonphthalein dye was 5 per cent in the first 15 minutes after in-

travenous injection of 1 c.c. The electrocardiogram was normal. A routine chest plate showed one cavity in the right apex and another in the left lower lobe. Two sputum examinations were negative for tubercle bacilli.

He was followed periodically until his death from uremia, four years later. Twenty-one serum uric acid determinations were performed during this period of time. The concentrations varied from 7.9 to 12.6 mg./100 c.c. The non-protein nitrogen concentrations varied from 60 to 150 mg./100 c.c. shortly before death. For a period of a few

FIG. 6. Roentgen-ray of foot of patient 2, at the age of 44. There is narrowing of the joint space of the metatarsal-phalangeal joint and a few osseous tophi. Compare this with figure 3.

months he was thought to have mildly active tuberculosis and sanatorium care was attempted. Because of a profound anxiety neurosis he was discharged home without having received any benefit. His gout progressed slowly but he had no more than three mild to moderate acute attacks per year. The roentgen-rays taken a few months before death showed a few additional changes associated with gouty arthritis. The clinical evidence of chronic joint disease was minimal. The blood pressure at the last admission to the hospital was 164 mm. Hg systolic and 114 mm. diastolic. He died in

uremia with pericarditis. The postmortem showed, in addition, mild coronary sclerosis, left ventricular hypertrophy and multiple cysts of the kidney. Microscopically, there was marked paucity of glomeruli of the kidney, increased fibrosis of the cortical areas and thickening of the vessel walls. A few of the tubules contained urate crystals. No specific pathological diagnosis of the renal lesion was made.

FIG. 7. Roentgen-ray of right foot of patient 3. The only gouty abnormality is an area of diminished density at the base of the proximal phalanx of the first toe.

Comment. This patient had renal disease, presumably an acute nephritis followed by a chronic stage, 10 years before his first attack of gout. His gouty arthritis was mild to moderate at all times. He died at the age of 43 in uremia. It is admittedly a temptation, to call this gout secondary to renal disease. It is the belief of the author, however, that it is gouty arthritis superimposed upon preëxisting renal disease, or renal disease associated with metabolic gout and eventually gouty arthritis.[4] If gout were caused by an

impaired ability of the kidney to excrete uric acid, one might expect more extensive deposits of uric acid in bones and soft tissues after a 20-year period of renal dysfunction. The duodenal ulcer, anxiety neurosis and pulmonary tuberculosis were believed to have been unrelated to the gouty arthritis. In the series of patients with gout followed in this clinic, a frequent association of gout and these several maladies has not been observed.

FIG. 8. Roentgen-ray of second, third and fourth metatarsal-phalangeal joint of the right foot of patient 4. Typical osseous tophi are seen.

Case 4. B. S., a white male, was seen first at the age of 50. He stated that the first joint symptoms, acute arthritis of the great toes, appeared at the age of 41. During the subsequent six years he had one or more acute episodes each year. The shoulders and knees were the site of attacks as well as the hands and the feet. Colchicine was prescribed in the early years and although it was not taken regularly it helped a great deal when full doses were ingested. He was symptom-free between attacks until the age of 49. At this time he noted persistent limitation of function of

shoulders and knees and constitutional symptoms, particularly malaise. On physical examination he had peri-articular swelling and limitation of motion about the shoulders, knees and ankles. There was spindling of the fingers, atrophy of the interosseous muscles and brown pigmentation of the hands. He had a low grade fever and a tachycardia. The roentgen-rays showed many typical findings of gouty arthritis (figure 8) and except for osteoporosis nothing to suggest rheumatoid arthritis. A biopsy of a

FIG. 9. Roentgen-ray of left foot of patient 5. Minimal changes associated with gouty arthritis are noted, i.e., an area of diminished density in the terminal phalangeal joint of the great toe.

nodule from the elbow showed the typical structure of a rheumatic or a rheumatoid lesion. There was complete absence of foreign body giant cells which may be seen in gouty tophi. He responded moderately well to full doses of colchicine but this drug had no effect upon the function of the chronically involved joints. A short time after discharge he had an acute attack of arthritis in his great toe. This subsided with colchicine. Subsequently, he was started on gold therapy and physiotherapy in addition to colchicine. These have helped him considerably and now he is back at work.

Comment. The association of gout and rheumatoid arthritis is an uncommon occurrence; some even deny the association.[2] When it is suspected, a difficult problem in diagnosis and treatment is presented. The development of the two conditions in one patient is probably coincidental and it is not thought that either disease predisposes to the other. The several diagnostic criteria for gout are satisfied in B. S.: history of acute attacks in peripheral joints, response to colchicine and typical roentgen-ray findings nine years after the onset of symptoms. Likewise, the diagnosis of rheumatoid arthritis seems justified on the basis of involvement of central joints, clinical appearance of affected joints, and the pathological examination of the nodule. Colchicine continues to be effective in the treatment of his acute attacks but more important now is the treatment of his presumed rheumatoid arthritis.

Case 5. B. C., a white male, was seen first at the age of 59. He denied having had any acute attack of joint disease prior to the age of 56. At the age of 19 he had an injury to his left hand and broke several fingers. They remained in flexion. The first attack of acute arthritis was in the knee which was swollen and red. A diagnosis of 'water on the knee' was made but aspiration was not performed. At the time of admission he complained of severe pain in the right hand that had not responded to hot soaks. On physical examination the blood pressure was 118 mm. Hg systolic and 76 mm. diastolic. There was a small tophus in each ear. The left hand showed the flexion deformity; the right hand was diffusely swollen, red and tender. The rectal temperature was 100.6° F. The physical examination was otherwise negative. The concentration of serum uric acid was 7.9 mg./100 c.c. and non-protein nitrogen 28 mg./100 c.c. The excretion of phenolsulphonphthalein dye was 19 per cent in the first 15 minutes and a total of 66 per cent in two hours after intravenous injection. The routine urine examination was negative. The roentgen-rays of the hands showed a few punched-out areas in the metacarpal-phalangeal joints and the flexion deformities. The roentgenograms of the feet showed minimal changes attributed to gout (figure 9).

In the next four years he took one colchicine pill each day and had three mild attacks of acute gouty arthritis. He died at the age of 63 of an acute myocardial infarct. This was not anticipated in that he had no previous symptoms suggestive of coronary heart disease.

Comment. This is an instance of minimal gouty arthritis with the first joint symptoms appearing at the age of 56. When seen less than three months after the first attack he had evidence by roentgen-ray of gout in the joints. The joint involvement was never a serious problem and death was caused by a myocardial infarct. Although the presence of irreparable gouty changes and subcutaneous tophi have been reported in association with the first attack of gouty arthritis, this is not the usual finding. Generally, patients have had joint symptoms for several years before tophi appear or roentgen-ray evidence of osseous tophi is demonstrable. Patient 8 is included to further illustrate this phase of the subject.

Case 6. F. P., a white male, was first seen at the age of 62 complaining of acute arthritis in the right foot of four days' duration. At the age of 50 he passed some gravel in his urine following pain in the right flank, chills and fever. He had three more episodes of passing gravel in the following 10 years. In one instance, the gravel

was analyzed and showed a high content of uric acid. His first attack of arthritis in the foot was four years after the first passage of gravel. The great toes were usually the site of acute arthritis which appeared in subsequent attacks about once a year. Redness, tenderness, swelling and heat in his right great toe were noted on physical examination. The blood pressure was 190 mm. Hg systolic and 108 mm. diastolic. There were no other significant findings. Several urine specimens were negative for

FIG. 10. Roentgen-ray of foot of patient 6, who had intermittent attacks of gouty arthritis for six years. No evidence of gout in the roentgen-ray.

albumin, casts and cells. The excretion of phenolsulphonphthalein dye was 30 per cent in the first 15 minutes. The roentgen-rays of the feet were negative for osseous tophi (figure 10). Minute areas of rarefaction were seen in the heads of the proximal phalanges of the third, fourth and fifth fingers on the right. The patient died at the age of 66 having had one or two attacks of gout annually. In many instances the attacks would follow a single drink of whiskey or wine. His consumption of colchicine tablets between attacks was approximately three per week. He continued to pass

gravel. The level of his serum uric acid varied from 6.2 to 12.4 mg./100 c.c. and the non-protein nitrogen from 28 to 34 mg./100 c.c. Death followed several weeks of cardiac failure from arteriosclerotic heart disease.

Comment. The passage of urate stones or gravel by gouty patients is seen occasionally. Hench [5] gives the incidence of gravel or stones as 13 per cent. In at least one other patient in our series, uric acid gravel was passed several years before the onset of joint symptoms. The development of urate stones after onset of joint symptoms does not appear to be directly related to the severity of renal disease. In a limited number of patients, the reverse appears to be true; if urate stones are found, renal impairment is not severe.

Another relevant aspect of urate stones is their spontaneous appearance in persons who do not develop gouty arthritis at some later time. The patients that have been followed for several years who have passed uric acid stones and who have had a normal serum urate have not developed gouty arthritis or an elevated serum urate subsequently. It cannot be denied that each person is not in the pre-arthritic stage of gout and will not develop gouty arthritis in the future. It is the belief of the writer, however, that this will not prove to be a fact and that urate stones do not necessarily mean gout. It is hoped that some investigator will report a long-term study of patients with urate stones who do not have metabolic gout or gouty arthritis at the time of observation. Determination of the urinary excretion of uric acid in such persons would be extremely valuable.

Case 7. P. D., a white male, who was first seen at the age of 57, had his initial attack of gouty arthritis in the right great toe at the age of 54. Each year thereafter he had an attack in the shoulders or feet which kept him in bed two or three days. The physical examination was negative except for Dupuytren's contractures of both hands. The urine examination was negative. The serum uric acid was 8.2 mg./100 c.c. The roentgen-rays of the hands and feet showed only one area of diminished density at the base of the proximal phalangeal joint of the right great toe. During the next four years he took one or two colchicine tablets each day as a prophylactic procedure. In this period of time he had one mild attack which was abated with a total of four colchicine tablets and one severe attack which required 12 tablets.

Comment. This patient illustrates the typical findings in a mild case of gout. The joint symptoms appear in middle life, the disease is not incapacitating, demonstrable sequelae do not develop and the joint symptoms are controlled with hourly doses of colchicine during acute symptoms and a few colchicine tablets per week in the symptom-free periods.

Case 8. P. W., a 45-year old white male, was seen for an unexplained tender left foot which began five weeks before admission following minor trauma to the instep. The patient continued to work for four days but was uncomfortable. He was then forced to use crutches and did not work for 10 days. Low grade symptoms persisted for the next two weeks and he used crutches intermittently. Finally, he was referred to the hospital for injection of the sympathetic nerves. He refused this procedure after admission because he had improved slightly upon bed rest.

On examination the foot demonstrated the cardinal signs of inflammation. The serum uric acid was 7.4 mg./100 c.c. The roentgen-rays of the feet (figures 11 and 12) showed some decalcification in the affected foot only and one area interpreted as

an osseous tophus that was not present in the roentgenogram taken at the time of the onset of symptoms. The decalcification was attributed to the partial disuse during the intervening five weeks. The other laboratory studies were negative except for a leukocytosis. The patient was given colchicine, 0.5 mg. every hour, for 12 doses at which time gastrointestinal distress developed. Colchicine was then stopped and Tinct. Camph. Opii., 4 c.c. was given. The patient had one loose stool. At the time the last dose of colchicine had been ingested the pain in the foot had lessened considerably. Twenty-four hours later he was able to stand on the foot. Two days later he was walking normally. The only evidence of previous inflammation was slight edema of

FIG. 11. (Left) Roentgen-ray of left foot of patient 8. Decalcification only is noted.
FIG. 12. (Right) Roentgen-ray of left foot, taken five weeks later than that shown in figure 11. An area of rarefaction is seen in the metatarsal-phalangeal joint.

the foot and beginning desquamation. The patient was advised to eat a balanced diet, keep his weight on the low side of normal, drink an abundance of fluids, and to take one or two colchicine tablets per week. During the intervening 18 months there was no return of acute arthritis.

Comment. The precipitation of an attack of acute gout by trauma is seen from time to time. In this instance the correct diagnosis was not made for five weeks and gout was not suspected until several other therapeutic procedures had failed to correct the disability. This patient was thoroughly studied and no evidence of permanent damage from metabolic gout was observed in other organs of his body. Following the attack he would be con-

sidered a normal healthy person in all respects except for the metabolic changes associated with gout.

Summary

Selected items from the medical study of eight patients with gout are presented. They serve to illustrate the diversity of gout and gouty arthritis.

The onset of symptoms, i.e., the first attack of gouty arthritis may appear in the first decade of life or as late as the eighth decade.

At the time of the first attack roentgen-ray evidence of osseous tophi or subcutaneous tophi on inspection usually is lacking.

The passage of urate stones or urate gravel may precede the first attack of gouty arthritis. Urate stones may be passed by persons who do not develop gouty arthritis subsequently.

Renal disease is the most important non-arthritic phase of gout. There appears to be no close correlation between renal involvement and joint involvement. The pathological findings in the kidney of gouty patients are a mixture of several entities.

Rheumatoid arthritis and gout may be observed in the same patient. Each disease must be treated independently. This may be done without aggravating either condition.

Colchicine 0.5 mg. per hour is recommended for the acute attacks. This dosage should be maintained until onset of gastrointestinal distress. From 10 to 14 doses are usually sufficient. Colchicine is then stopped and Tinct. Camph. Opii. is given.

Between attacks some colchicine is recommended. In patients with frequent attacks of arthritis, one or two colchicine tablets each day is advised. Less severe cases may require but one or two tablets per week.

A balanced diet with a liberal fluid intake seems to produce as satisfactory results in many patients as does rigid dieting.

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ELECTRON MICROSCOPY IN RELATION TO THE MEDICAL SCIENCES *

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"L'infinité de la petitesse," in the words of Blaise Pascal, includes extensive areas whose submicroscopic dimensions render them inaccessible to light microscopy but which are accessible to exploration with the electron microscope. It is the purpose of the present article to survey very briefly these areas within the medical sciences. For those who wish to search the literature in whole or in part a bibliography is appended; preference is given to more recent and more comprehensive articles in which earlier studies are cited.

The electron microscope [1] is a modern device for obtaining optical images of objects particularly of submicroscopic dimensions. Illumination is by a beam of electrons focused by a system of electromagnetic lenses analogous to the glass lenses of a microscope. Accurate imaging of details of pattern down to about 0.2 μ are obtainable with the light microscope. Under appropriate conditions the electron microscope is currently giving accurate pictures of fine structure down to 0.01 μ diameter in organic material [2, 3]; dense particles of 0.002 μ diameter can be resolved.

The region of fine dimensions which is inaccessible to light microscopy but accessible to electron microscopy has already been shown to comprise structural details of bacteria,[3-8] rickettsiae, [9-11] viruses [12-29] and bacteriophages,[30-37] the fine structure of protoplasmic fibrils and fibrous structures,[38-49] macromolecular-scale structure within appropriately prepared tissue culture cells,[50-54] the submicroscopic organization of liver, nerve, muscle and other tissue [55-59] and chromosomes,[60-62] chloroplasts,[63] mitochondria [64] and colloidal molecules and particles.[65-68] Electron microscopy on the American continent is only about 10 years old; with advancing technics even wider prospects will unquestionably open up, in particular through the use of the electron microscope in parallel with longer known research instruments and procedures.

In all bacteria, cell wall [4, 69] and inner protoplast with limiting plasma membrane, and in various species, extracellular capsules,[70] flagella,[4, 8, 71] and developing and mature spores [5, 6] have been clearly visualized. The bacterial nucleus [3, 72] and even macromolecular scale fine structure within protoplast,[3] cell wall and spore coat [6] have been visualized also, albeit still with technical problems as limiting factors. Certain bacteria have long been known to possess the remarkable biochemical capacity of synthesizing living protoplasm from the simplest source materials; such bacteria are now shown to be

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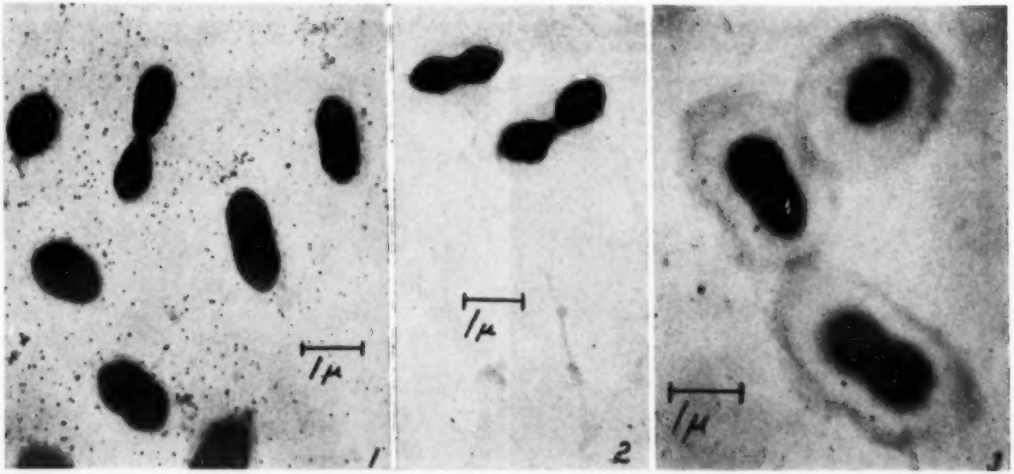

1—*Diplococcus pneumoniae*, type 3.
2—*Diplococcus pneumoniae*, type 3 in type 1 serum.
3—*Diplococcus pneumoniae*, type 1 in type 1 serum.

FIG. 1. The pneumococcal capsular swelling reaction. Reproduced from MUDD, S., HEINMETS, F., and ANDERSON, T. F.: Jr. Exper. Med., 1943, lxxviii, 327–332. Prints for figures 1 to 4 inclusive furnished by Committee on Materials for Visual Instruction in Microbiology, Society of American Bacteriologists; Dr. Harry E. Morton, Chairman, University of Pennsylvania.

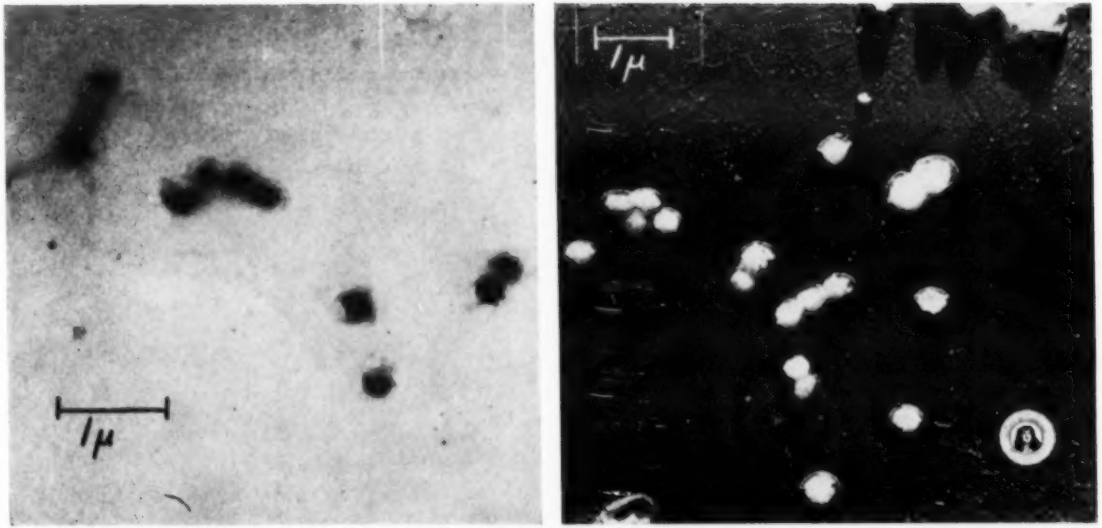

FIG. 2. Virus elementary bodies of feline pneumonitis. Unshadowed pictures on left from RAKE, G., RAKE, H., HAMRE, D., and GROUPÉ, V.: Proc. Soc. Exper. Biol. and Med., 1946, lxiii, 489–491. Gold-shadowed elementary bodies on right from HAMRE, D., RAKE, H., and RAKE, G.: Jr. Exper. Med., 1947, lxxxvi, 1–6.

morphologically complete cells with characteristics convenient for direct electron microscopic investigation of the structure and organization of protoplasm in this relatively simple form.

Antibodies have been made visible in combination with the surface structures of bacteria and viruses. Antibodies combine chemically with and form a surface deposit on cell wall and flagella of non-capsulated bacteria [4,73] and on the surfaces of virus particles.[26, 74, 75] In the case of virulent pneumococci, antibodies and other serum proteins permeate and swell the extra cellular capsule.[76]

Certain germicides may readily penetrate the bacterial cell wall and attack the plasma membrane.[77, 78] Antibiotics [36, 79-82] may inhibit cell division and result in morphological aberrations or in bacteriolysis. Morphological difference in the nucleus in phase variants has already been reported.[83] Study by light and electron microscopy of the bacterial nucleus in relation to genetic change and to the action of mutation-inducing physical and chemical agents is a fascinating problem to the threshold of which current advances in the cytology and genetics of microörganisms and the technics of electron microscopy [84-87] have just brought us.

The electron microscope has made a peculiarly valuable contribution to the study of the rickettsiae and viruses, which are near or beyond the limits of resolution of the light microscope. The rickettsiae, viruses of the lymphogranuloma-psittacosis group,[27-29] and the pox viruses [13, 24-26] have been shown to have the structure of very simple cells equivalent to that of tiny bacteria. The cell wall and protoplast may be differentiated, and in vaccinia there has even been described what appears to be a nucleus.[88] The influenza virus, which is quite invisible with the light microscope, has also apparently a surface membrane and inner protoplasm. The particles of bacteriophage, which are often considered as viruses parasitic upon bacteria, are usually tiny sperm-shaped particles containing a head of characteristic shape and a tail. The head of coliphage particles is of complex structure in that it contains a characteristic pattern of granules. The contents of the head, moreover, may be released and leave an empty envelope with tail attached.[89] The currently available evidence strongly suggests that the larger viruses, such as those of lymphogranuloma and psittacosis and of the pock diseases, multiply like bacteria by division, but that the most thoroughly studied bacteriophage particles are synthesized within the bacterial cell. The fact that phage-infection of a bacterial cell imposes a new metabolic pattern on the infected cell and results in the elaboration of multiple new infectious phage particles is a remarkable one, study of which may well afford clues to the understanding of virus-induced neoplasia. Colony-like groups of virus particles have been demonstrated in the cytoplasm of cells of virus-induced neoplasia.[51, 53]

Isolated virus particles under proper conditions have been shown by Wyckoff [22, 23] to form beautiful crystalline arrays in three dimensions. In general it may be said that the problem of visualizing any of the viruses is

primarily one of isolation and preparation. All can be clearly demonstrated by the electron microscope once they are isolated.

Protoplasmic fibrillar structures have lent themselves particularly well to structural analysis by the electron microscope in parallel with studies by polarized light, x-ray diffraction and other physical and chemical means. Beautiful periodic regularities in ultrastructure have been demonstrated by

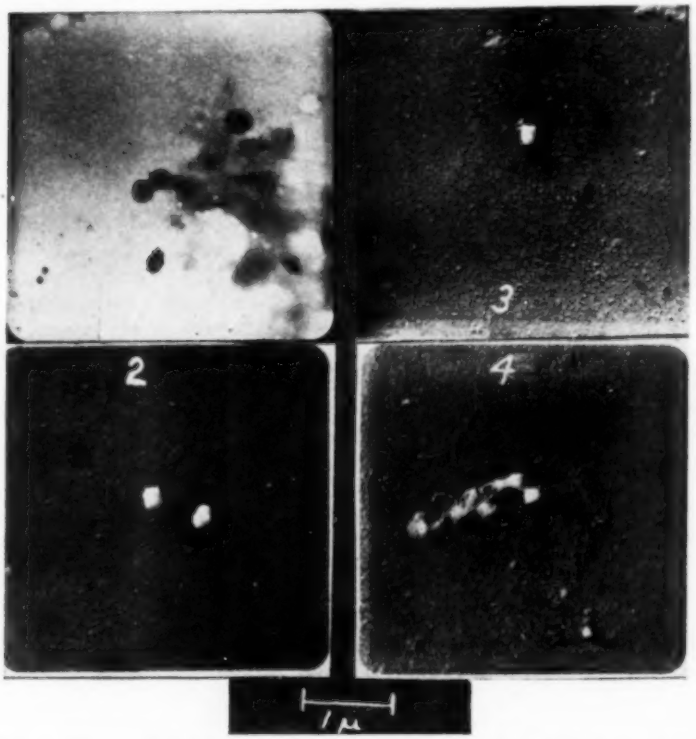

FIG. 3. Viruses of variola (1 and 2) and varicella (3 and 4) from human cases; 1 unshadowed, 2–4 shadowed with gold. From NAGLER, F.P.O., and RAKE, G.: Jr. Bact., 1948, lv, 45–51.

Schmitt, Hall and their collaborators in connective tissue,[39, 41, 42, 47] muscle [43–45] and nerve fibrils [48, 49] and in their component proteins. A foundation knowledge of normal ultrastructure is being laid for later comparison with ultrastructure in such pathological conditions as the collagen diseases, and nerve and muscle inflammations and degenerations.

The scope of useful applications of the electron microscope in the medical

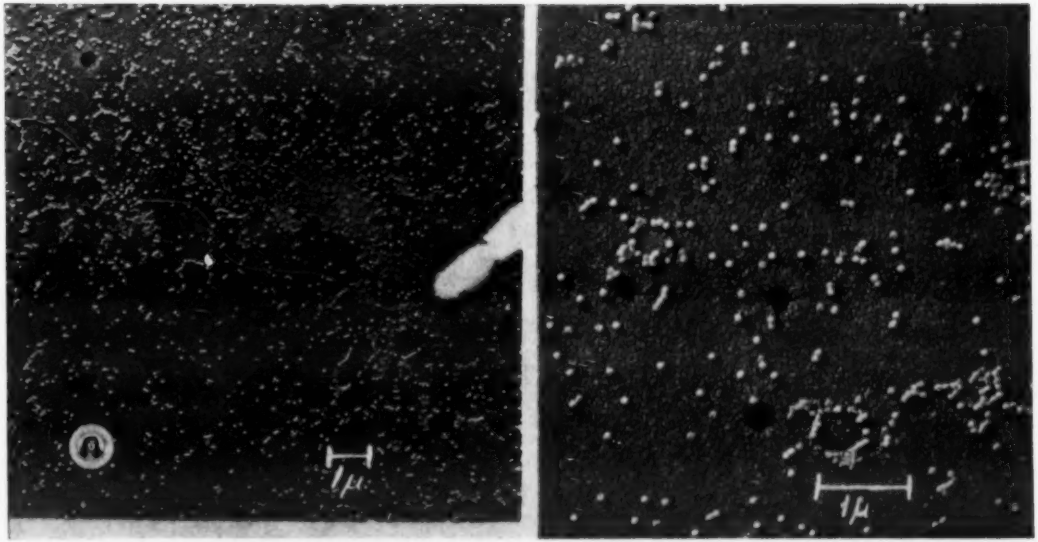

FIG. 4. Rabbit papilloma virus shadowed with gold. In the picture on the left a bacterium with terminal flagellum is included to illustrate minute size of these virus particles. From SHARP, D. G., TAYLOR, A. R., HOOK, A. E., and BEARD, J. W.: Proc. Soc. Exper. Biol. and Med., 1946, lxi, 259–265.

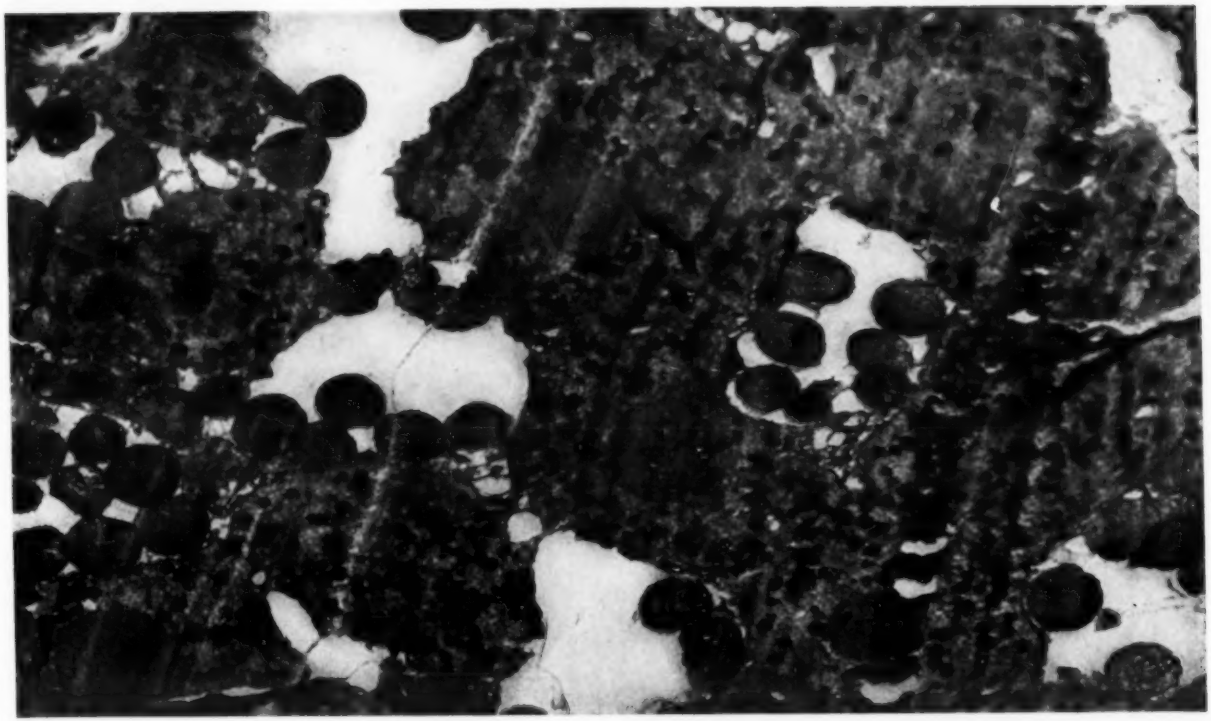

FIG. 5. Thin section through rat liver. Cell walls, nuclei, nucleoli, mitochondria, bile capillaries, and blood sinusoids are visible. Sections of red blood cells appear in some sinusoids, although most were removed by the perfusion technic employed in the initial fixation with osmic acid. From PEASE, D. C., and BAKER, R. F.: Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 470–474.

sciences has been broadened steadily by the development of new technics both preparative and instrumental. Tissue culture cells, their components and inclusions are being rendered accessible to investigation through technics under development by Claude and Porter.[50-54] Regularities of internal structures of collagen, muscle, nerve and fibrin fibrils have been revealed through adaptation of fixation, "electron staining" and shadowing procedures.[39-49] Metallic shadow casting [20] has increased contrast and has made possible the imaging of minute structures in three dimensions. Technics of surface replica which have had wide application in metallography, mineralogy, etc. are being applied to the study of biological surfaces.[47, 54, 62, 90]

Incomparably the greatest broadening of applications of electron microscopy has been made possible by the elaboration of methods for cutting thin sections of tissue. Early work by O'Brien and McKinley [91] has been followed by the construction of a high speed microtome [92] capable of cutting sections of the order of 0.1 μ in thickness. Studies of such sections of various tissues including neoplasia are appearing.[55-57] Most recently D. C. Pease and R. F. Baker [58, 59, 61] of the University of Southern California, employing double imbedding in collodion and paraffin and a special adapter to the conventional microtome, have cut and made beautiful electron micrographs of sections of liver, muscle, nervous tissue and chromosomes only 0.05–0.10 μ in thickness. This technical achievement makes accessible to electron microscopic study the enormous field of the fine structure of normal and pathological tissues.

Because of the newness of electron microscopy, the high cost of the instrument and the expertness required for proper maintenance, operation and interpretation, the electron microscope is certainly not now, nor is it likely to become soon, an office instrument. A beginning has been made, however, in application of electron microscopy to the differentiation of certain related viruses.[26] Such uses and the newly developing technics of preparing tissue sections will probably soon give electron microscopy areas of application in diagnostic laboratories in the larger hospitals and institutes. The prospect which is most exhilarating, however, is that of pure scientific research, the exploration of one, possibly two new orders of magnitude of fine dimensions by electron microscopy supplementing other current research instruments and technics.

On the grave of John Herschel in Westminster Abbey is the inscription:

> "Joannes Herschel, Gulielmi Herschel natu, opere, fama, filius unicus,
> 'coelis exploratis,' hic prope Newtonum requiescit.
> Generatio et generatio mirabilia dei narrabunt."

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PHARMACODYNAMICS OF PULMONARY ABSORPTION IN MAN. I. AEROSOL AND INTRATRACHEAL PENICILLIN *

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Direct medication of the pulmonary epithelium is not a new development in therapeutics. It is readily understandable why interest in this accessible direct route of therapy should have developed during the early attempts to treat pulmonary disease. With the advent of successful specific oral and parenteral therapy, however, interest in primary medication of the lungs began to lag. The musculotropic and neurotropic action of bronchodilators, the belladonna group of alkaloids, and others, on the musculature and secretory cells of the bronchi was striking. Even more striking, however, was the immediate and prolonged relief afforded the asthmathic by the inhalation of adrenalin mist. This was probably the first method of directly treating pulmonary structures which became widely accepted.[1]

It was not until the advent of chemotherapeutic and biotherapeutic agents, however, that interest in direct medication of diseased pulmonary tissue was revived.[2, 3, 4] The clinical demonstration that these agents, administered by the conventional routes, did not appear to affect beneficially walled off, poorly vascularized abscess cavities intensified this interest. Finally, the development of small, efficient nebulizers and new technics of aerosolization [5] offered practical means of accomplishing effective direct medication of pulmonary structures.

In spite of much interest in this form of therapy during the past few years, the mechanism of drug and fluid absorption from and into the normal and diseased lung has been generally ignored. Chemotherapeutic and biotherapeutic aerosols have been given in a relatively small number and variety of vehicles. Common vehicles include bronchodilators, emulsificants, wetting agents and other bacteriostatic drugs. However, no comprehensive comparative studies have been made on the effect exerted by such diluents on penicillin absorption and excretion. Numerous types of aerosolizing apparatus and modifications have been described, but reports as to their relative efficiency vary widely. Comparison of their effectiveness is difficult to make since investigators, working with one or more apparatuses, have generally used different quantities of active agent and different methods of assaying activity.

It was, therefore, decided to undertake a comprehensive study of the

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pharmacologic and mechanical aspects of direct medication of the lung in man. Penicillin was chosen for this study for several reasons. It is, at present, the most frequently used agent in this form of therapy. It is free from serious toxic side reactions; it is not inactivated in the presence of pus; it is fairly stable in body fluids at freezing temperatures, and its assay in these fluids, although cumbersome, is readily accomplished by a trained bacteriologist.

The various factors requiring study are: (1) the pharmacodynamics of absorption and excretion following intratracheal and aerosol administration as contrasted to parenteral administration; (2) the action, if any, of various vehicles, other than saline, on absorption; (3) the effect of suppuration of the lung on the absorption mechanism; and lastly, (4) the relative efficiency of various methods of aerosolizing therapeutic agents. This report deals with the pharmacodynamics of absorption and excretion from the normal human lung.

Absorption from normal alveoli involves a more complex mechanism than absorption from muscle or subcutaneous tissue. Fluids must pass through the epithelium-lined wall of the alveoli and then cross the endothelium-lined capillaries into the blood stream. An alternative route is presented by the endothelium-lined lymphatics with which the alveoli are richly supplied. It is well known that fluids are absorbed from the bronchioles, bronchi and even the trachea. The relatively small surface area of the tracheobronchial tree as compared to that of the alveoli, makes absorption from the tracheobronchial mucosa quantitatively unimportant. As previously mentioned, the literature contains few references to the manner in which molecules of various sizes are absorbed from the lungs. The only studies recorded have been made in relation to war gas poisoning, pulmonary edema, and in Drinker's fundamental work on the lymphatic drainage of the lungs. Winternitz and Smith,[6] after the First World War, demonstrated that physiologic saline was rapidly absorbed when injected into the trachea of anesthetized dogs. Phenolsulfonphthalein, similarly administered, appeared almost immediately in the urine. Courtice and Phipps,[7] more recently in the course of studies with phosgene poisoning, administered water, physiologic saline and serum endotracheally to anesthetized rabbits and dogs and collected the flow from the right lymphatic duct in the latter. They were able to calculate the amount of fluid absorbed from the lungs by comparing the normal heart/lung weight ratio to that found after sacrificing the experimental animals at various intervals. Figure 1, taken from their article, illustrates their findings: 80 per cent of the water and 23 per cent of the saline were absorbed within the first hour. Serum absorbed very slowly, about four days being required for complete removal of all the material. The lymph flow was not appreciably increased above the normal; thus very little of this fluid was absorbed by the lymphatics. The ease with which water and molecules the size of sodium chloride and even phenolsulfonphthalein are absorbed from the lung is now evident. Drinker[8] in similarly arranged experiments,

demonstrated the ease of absorption of a 1 per cent aqueous solution of Evans Blue (T–1824, a dye with a fairly large molecular weight). Direct blood capillary absorption from the alveoli was demonstrated since the plasma became blue even when both the right lymphatic and thoracic ducts were cannulated. The lung lymphatics were shown to offer a further route of absorption, inasmuch as the right duct lymph became deeply blue. When the dye was vaporized in watery solution and the blue mist inhaled by the animal, the plasma soon became blue. Cannulation of the right lymphatic duct again showed dye absorption, but this quantity was considered insignificant as compared to that absorbed directly into the blood. T–1824 was

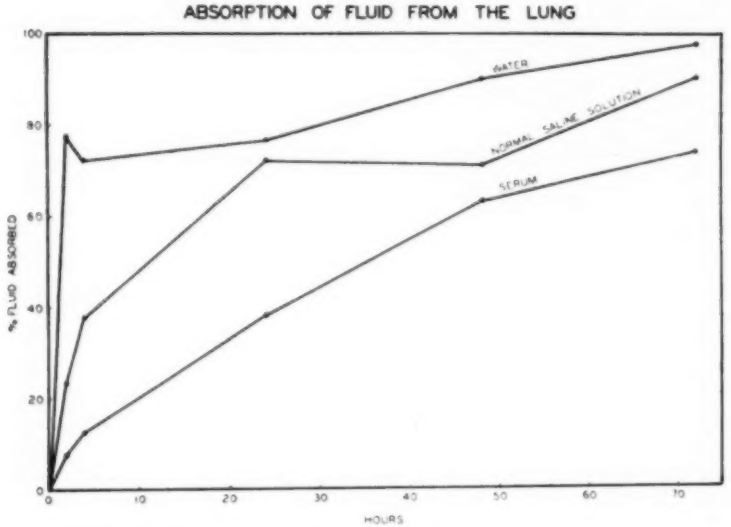

FIG. 1. Absorption of fluid from the lung. (After Courtice and Phipps, 1946. Courtesy of the Journal of Physiology.)

then instilled into the trachea in a 1 per cent solution dissolved in dog plasma and no dye appeared in either the blood or the lymphatics during the course of four hours. Since the dye has been shown to combine with the albumin molecule,[9] this further confirmed the slow absorption of serum from the lung. Apparently the alveolar wall presents an effective barrier to molecules over a certain size. Purified bovine serum albumin, crystallized egg albumin and hemoglobin were shown by Drinker to enter the lymphatics in traces only and, to an even lesser extent, the blood capillaries. He suggested that the molecule of penicillin, which is much smaller than that of egg albumin, might freely enter the blood stream from the alveoli.

A rational approach to the study of absorption and excretion of penicillin administered by the aerosol route necessitates an accurate determination of the amount of the active agent which actually reaches the pulmonary epithelium. It would seem, at first, that this amount might be calculated by comparing the total urinary excretion of the intramuscularly administered penicillin to that excreted following aerosol administration. If no penicillin were inactivated or detoxified within the body, such a comparison would hold. However, it is well established that only 40 to 60 per cent of parenterally administered penicillin can be recovered from the urine.[10, 11, 12] Moreover, the processes by which the balance of the biotherapeutic agent is detoxified or inactivated and the organs involved in this mechanism have not been established. Penicillin given intravenously to patients with complete renal shutdown disappears from the blood at a logarithmic rate with a half-life of about two hours.[13] Any interference with urinary excretion, due to renal insufficiency or drugs competing with penicillin for tubular excretion, such as diodrast, p-aminohippuric acid, caronamide, and others, may reduce the percentage of excreted penicillin in the urine to 30 per cent or less.[12, 14, 15, 16] Thus it appears that the amount of penicillin excreted is inversely related to the time of exposure within the body as a whole.

It also seems apparent that the capacity of the specific organ (the site of administration) to inactivate penicillin will inversely affect the urinary excretion. The influence of muscle or gastrointestinal mucosa on penicillin has been well established, but the effect which the pulmonary epithelium exerts is not known. It would, therefore, appear desirable to administer the drug into the tracheobronchial tree in such a fashion that no losses occur. If the percentage of urinary excretion under such conditions were known, a comparison with the excretion of aerosolized penicillin would be valid, and the effectiveness of this latter mode of administration could be calculated. Large losses with inhalational administration may be expected, largely due to technical difficulties. Loss in the apparatus and in the mouth can be relatively easily determined, as described elsewhere.[17] However, it is not so easy to determine the amount of active agent lost to the outside air. This loss may be expected to be the largest due to the following: (1) part of the inspired air (the dead space air) does not reach the alveoli and, therefore, most of the fluid particles are not removed; (2) the smallest droplets may enter the alveoli and leave them again on expiration without having been deposited; and (3) prevention of some loss to the outside air during aerosolization is impossible. A quantitative basis for the study of absorption and excretion following pulmonary administration requires a method by which the above mentioned losses are eliminated. We therefore elected to administer penicillin solution directly into the tracheobronchial tree by endotracheal catheter.

Methods

The procedure used for endotracheal catheterization was identical to that used by the Thoracic Surgical Service to instill radio-opaque oil for

bronchography. Nembutal 0.1 gm., was given on the eve of, and again two hours before the procedure, to reduce the incidence of reactions to the topical anesthetic.[18] Breakfast was withheld and 60 mg. of codeine were given prior to intubation. A syringe with 0.3 gm. of Sodium Luminal in solution was on hand at all times to combat reactions (none occurred). The oropharynx was sprayed lightly with a 2 per cent Pontocaine solution (tetracaine) and a No. 12 French urethral catheter was passed through the nostril into the trachea during deep inspiration. Pontocaine, 4 c.c. of a 0.25 per cent solution, was instilled immediately and again five minutes later, after the catheter had been withdrawn sufficiently to assure the position of its tip above the carina. No more than a total of 2 c.c. of the 2 per cent solution (0.04 gm.) was used at any time. Cough was then encouraged to insure even distribution of the anesthetic solution throughout the tracheobronchial tree. Within a few minutes, the cough reflex was completely abolished. One hundred thousand units of Crystalline Penicillin G Potassium in 10 c.c. of saline were then injected through the catheter while the patient assumed various positions designed to effect an even flow of the penicillin solution throughout his lungs.

Nine patients were treated in this fashion. Blood was withdrawn at one half-hour, one hour and every hour thereafter for six hours and occasionally up to 10 hours. Urines were collected at one, two, four, eight and 24 hours and assayed separately.

To compare the results of parenterally administered penicillin, 10 volunteers were given 100,000 units intramuscularly and bloods and urines were assayed similarly. This was done to avoid errors of comparison which might arise from variations in both our technic of penicillin assay and the type of penicillin used and those of other workers.

For the aerosol studies, the Vaponefrin nebulizer with an attached, humidified, rebreathing bag was used. Of various apparatus combinations tested, this gave the most consistently high blood levels.[17] Apparatus and mouth rinses were assayed to estimate measurable wastage.

Using Rammelkamp's strain of highly penicillin sensitive beta hemolytic streptococci (No. 98), we determined the penicillin levels by his serial dilution method.[19] The only modification was the use of Group O human red blood cells as an indicator instead of horse or sheep cells, in order to avoid hemolysis.[20] The smallest amount of penicillin definitely detectable by this method was 0.019 unit per c.c. of serum. In the lowest dilutions, the problem of the inactivation of penicillin by serum arises.[21] In the first tube, the serum concentration by this method was 28 per cent. According to Eagle's chart,[22] a multiplication factor of 1.5 was necessary to obtain the correct value for the penicillin G content of this first indicator tube. Since most of the literature on penicillin sensitivity was written before this was generally understood, we have omitted this correction factor intentionally. In all the other dilutions except the first, this factor becomes unimportant since broth was used throughout for dilutions. Bloods and urines were

refrigerated for no longer than 24 hours. Storage for longer periods of time caused a loss in penicillin activity detectable by this method. Urines were not buffered since it has been shown that penicillin excreted in the urine is more stable than commercial penicillin and will tolerate a pH as low as 2.2 for long periods of time.[23] This method of assay is no more accurate than other methods of biological assay involving serial dilution. Each numerically expressed level signified that the specimen contains about half as much active substance as would be needed for a positive reaction in the next tube. In order not to give a false impression of accuracy, we have used the values of 0.16, 0.08, 0.04, 0.02, etc., rather than the values obtained by serially dividing 20 (the number of units per c.c. of standard) by 2, namely 10.... 2.5....0.625....0.156, 0.078, 0.039, 0.019.

Results

A total of 297 specimens were assayed, of which 167 were bloods, 108 urines and 22 apparatus and mouth rinses. Ten volunteers received 100,000 units of penicillin intramuscularly in 1 c.c. of saline (chart 1). The results

Chart 1

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Saline by the Intramuscular Route in 10 Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
No. 1	1.25	.63	.08	—	.02	—	—	24,960	5,070	—	390	27
No. 2	.16	.16	.08	—	—	—	—	—	—	—	—	—
No. 3	.31	.63	.31	.08	.04	.02	.00	4,368	10,250	13,750	2,340	300
No. 4	.63	.31	.08	.04	.00	.00	.00	72,500	10,750	4,750	796	900
No. 5	1.25	.63	.31	.08	.04	.00	.00	18,750	4,750	12,250	—	250
No. 6	2.50	1.25	.16	.08	.00	.00	.00	22,500	6,250	14,750	—	1,875
No. 7	1.25	.63	.23	.08	.02	—	—	17,750	3,750	4,368	725	204
No. 8	.63	.63	.16	.08	.02	.02	.00	31,500	12,000	2,934	897	31
No. 9	1.25	.63	.16	.04	.00	.00	.00	35,500	11,500	1,248	117	24
No. 10	1.25	.63	.31	.16	.04	.02	.00	35,250	19,375	4,992	702	689
Average	1.05	.61	.19	.07	.02	.01	.00	29,231	9,299	7,380	852	478
								(Total—47,240)				

varied somewhat from one individual to another but, on the whole, were fairly uniform. The highest blood levels occurred one-half hour after administration and the average level, at that time, was about 1 unit per c.c. of serum. A rapid decline followed and levels generally considered to be significant were maintained for three hours only. There was no evidence of any penicillin activity at the end of six hours in any of the blood specimens. The urinary excretion paralleled these blood levels very closely. An average of 29,231 units was excreted during the first hour with a rapid decline thereafter. The total average excretion, 47,240 units or 47.24 per cent, was slightly below the figure generally reported in the literature.

CHART II

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 10 c.c. Saline by Tracheal Catheter in Nine Normal Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 rh.	4 hr.	6 hr.	24 hr.
No. 1	.04	.04	.08	.08	.16	.04	.04	4,399	1,000	998	1,123	562
No. 2	.08	.08	.08	.08	.08	.08	.04	4,836	7,375	8,125	592	393
No. 3	.08	.16	.16	.08	.08	.08	.04	7,062	7,062	4,680	—	377
No. 4	.16	.08	.08	.08	.16	.04	.04	1,197	429	1,903	1,326	0
No. 5	.08	.16	.31	.31	.16	.04	.08	—	—	—	—	—
No. 6	.16	.16	.31	.04	.04	.02	.02	11,937	468	1,326	904	249
No. 7	.31	.31	.16	.16	.04	.04	.02	9,661	1,875	826	427	149
No. 8	.16	.16	.16	.08	.04	.04	.02	13,375	2,312	5,812	1,794	0
No. 9	.16	.16	.16	.08	.02	.02	—	12,000	1,250	5,000	4,682	200
Average	.14	.14	.17	.11	.08	.04	.04	8,060	2,721	3,365	1,545	241
									(Total—15,932)			

Nine subjects received 100,000 units of penicillin in 10 c.c. of saline by the endotracheal route (chart 2). No cough was evoked and thus, there was no loss of penicillin. The average blood level at one-half hour (0.14 unit per c.c.) was one eighth that obtained with the same dose administered intramuscularly. However, the abrupt fall in blood levels observed with intramuscular administration did not occur. On the contrary, the levels continued to increase and reached their peak (0.17 unit per c.c.) two hours after administration. At the end of three hours, the average level (0.11 unit per c.c.) was almost twice as high as the comparable intramuscular level (0.07 unit per c.c.) Significant blood levels (0.04 unit per c.c.) were

CHART III

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Physiological Saline by Oxygen Aerosolization in 12 Normal Subjects

	Blood					Urinary Excretion		
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	1 hr.	2 hr.	24 hr.
No. 1	.16	.16	.04	—	—	8,750	2,500	22
No. 2	.16	.08	.08	—	—	2,850	5,700	12
No. 3	.08	.08	.04	—	—	2,496	624	—
No. 4	.16	.08	.02	—	—	4,000	936	1,250
No. 5	.08	.08	.02	—	—	1,475	—	—
No. 6	.08	.04	.02	—	—	1,125	875	—
No. 7	.16	.08	.04	—	—	2,500	3,000	—
No. 8	.08	.08	.02	—	—	3,500	4,500	—
No. 9	.08	.08	.04	.02	0	3,159	2,496	1,748
No. 10	.16	.08	.04	0	0	546	507	—
No. 11	.16	.04	.02	.02	0	702	—	—
No. 12	.08	.08	.04	0	0	0	0	—
Average	.12	.08	.04	.01	0	2,592	2,113	758
							(Total—5,463)	

maintained for twice as long as with intramuscular administration (six hours). Urinary excretion correspondingly was much lower at one hour (8,060 units) and fell off less rapidly; almost an equal hourly amount was excreted from the second to the sixth hour. The total excretion of 15.9 per cent was roughly one third that obtained following intramuscular administration. These serum levels and urinary excretions are compared in figure 2.

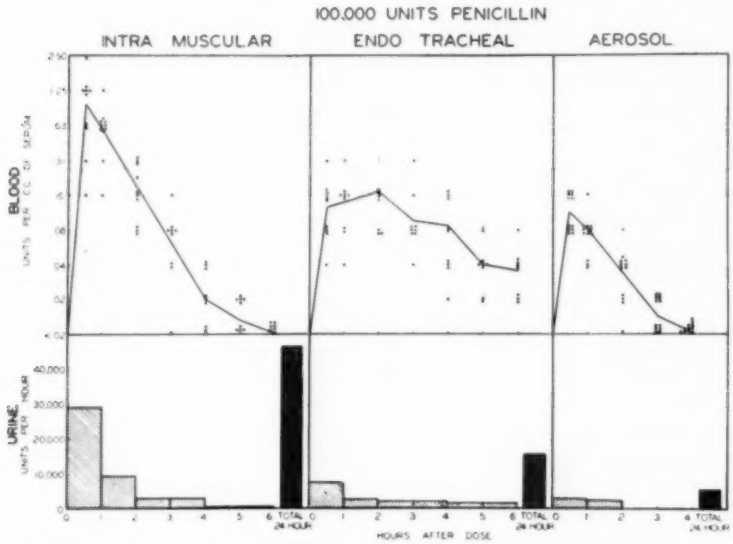

FIG. 2. Blood levels and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes in normal male subjects.

Twelve patients received 100,000 units of penicillin in 1 c.c. of saline by aerosolization with the nebulizer-rebreathing bag apparatus (chart 3). The average blood level at one-half hour (0.12 unit per c.c.) parallels the corresponding level following endotracheal injection. Although the average at two hours was 0.04 unit per c.c., five of the 12 serums showed less than this therapeutically effective amount. No significant levels were encountered after two hours. Thus, although the aerosol curve reaches almost the same peak as the endotracheal curve, it drops off more quickly. Urinary excretion corresponds very closely. The total excretion averaged 5.46 per cent, approximately one third of the endotracheal excretion. These relationships are illustrated in figure 2.

DISCUSSION

On comparing the parenteral and endotracheal blood level curves, several facts become evident. Absorption from the alveoli is much slower than from

muscle tissue. About 75 per cent of the administered dose is absorbed and excreted from intramuscular administration during the first hour; 97 per cent of the substance is excreted within the first four hours and only traces are discernible in the blood at the end of that time. Following intratracheal administration, the peak of absorption is not reached until two hours after administration; 83 per cent is excreted during the first four hours and even at the end of six hours, levels of therapeutic significance are still found in the blood. Thus, although penicillin absorption from the lung begins almost instantly after administration, the time required to remove all the substance from the lung is about six to eight hours, while muscle tissue can be freed of penicillin almost completely within relatively few minutes.

The lungs are estimated to contain 300,000,000 alveoli with a total surface of 65 square meters and lined with capillaries whose walls are only 0.000008 cm. thick.[24] In view of this, an enormous absorptive capacity should be expected and our results may appear surprising. Previous studies on the absorption of fluid from the lung, however, are confirmed. In Courtice and Phipps' absorption curve of physiologic saline from the lung (figure 1) absorption took place instantly after administration, but only 36 per cent was absorbed after four hours. Their value for speed of absorption is expectedly lower than ours since 10 c.c. of fluid in a rabbit lung are equal, relatively, to 20 to 50 times the same quantity administered to man. Fatal reactions that can occur within one to two minutes after intratracheal administration of cocaine or Pontocaine [18] illustrate the extremely rapid absorption of small quantities of hypotonic solution. Following the intratracheal administration of adrenalin, we have observed the onset of tachycardia within 30 seconds.[25]

Suspension of penicillin in oil or wax, with or without Procaine, or freezing the site of intramuscular administration, slows its absorption considerably. It would seem desirable similarly to slow the absorption of penicillin from the lung, since prolonged local concentrations are very desirable. This could be accomplished if it were possible chemically to combine penicillin with a molecule sufficiently large to prevent speedy absorption as outlined above. Over four years ago, Ingraham and Gaensler [26] attempted to slow intramuscular absorption by combining penicillin with human albumin and globulin fractions. They demonstrated that if such chemical combination were formed, it did not affect the rate of absorption. In another part of the present study,[25] similar negative results were obtained when penicillin in human plasma was administered to the lungs.

Total urinary excretion, following intratracheal administration, is one third that following parenteral injection. This may be anticipated since penicillin enters the blood stream more slowly; more of it, therefore, is detoxified or inactivated and less excreted. Delayed excretion by competitive inhibition of renal tubular excretion is another example of this phenomenon.

The well maintained high blood levels suggest the intratracheal route of administration as a therapeutically desirable one. To maintain effective

blood levels by this route, injections are necessary only one-half as often as a similar dose given parenterally. Several methods of endobronchial administration of penicillin have been previously suggested. Kay and Meade [27] injected 250 to 10,000 units in 3.0 to 5.0 c.c. of saline by indirect laryngoscopy through a laryngeal cannula, without anesthesia, and reported favorable results in ulcerative tracheobronchitis, minimal bronchiectasis, and in preoperative treatment. Moore and Thompson [28] treated severe bronchiectasis with bronchial lavage and intratracheal penicillin and sulfathiazole under nupercaine anesthesia. Bobrowitz et al.[29] gave six bronchiectatic patients 50,000 to 250,000 units a day by the supraglottic method of instillation following cocainization; they recorded rapid and satisfactory symptomatic improvement. Romansky [30] treated 12 cases of pulmonary suppurative disease with endotracheal penicillin suspended in iodized heavy oil.

We do not propose this form of treatment as a routine measure for several reasons. In order to obtain penicillin levels comparable to the ones we obtained, it is necessary to abolish the cough reflex by topical anesthesia. This not only introduces the well known hazards of topical anesthesia, but also violates an important therapeutic principle in the management of bronchopulmonary disease—maintenance of adequate cough reflex. This would be highly undesirable in the very diseases where primary application of penicillin to the tracheobronchial tree is indicated. Finally the technic of endotracheal intubation is more difficult and not as well tolerated by the patient as aerosolization.

In another study, dealing with absorption of penicillin in chronic suppurative pulmonary disease, we have consistently shown that parenterally administered penicillin does not reach the purulent sputum.[31] It has been the impression for some time that parenteral therapy will not penetrate the walled-off purulent cavity but will improve a surrounding pneumonitis.[27, 28, 29] Since the primary aim of penicillin administered directly to the lung is the production of high local concentrations, the nebulizer is the most practical tool by which the therapeutic agent can be placed at the site of the pathologic process. Endotracheal manipulation and topical anesthesia are not necessary. Most patients are easily taught to use the aerosol apparatus themselves in the hospital or at home. Furthermore, we have shown elsewhere that the amount of penicillin deposited in the lung, as evidenced by the penicillin excreted in the sputum, compares favorably with the endotracheal method. Our [31] experiences on the Inhalational Therapy Service and the Thoracic Surgical Service do suggest, however, that in certain special cases biotherapeutic agents may be given to great advantage by the endotracheal route. Such is the case when endotracheal intubation is necessary, primarily for other reasons, as at time of bronchoscopy or bronchography, during the course of endotracheal aspiration therapy following thoracic surgery, or in the treatment of acute atelectasis. Our experiences also suggest that when a rapid and striking reduction of sputum is necessary prior to surgery for sup-

purative disease of the lung, endotracheal therapy will produce this change in the shortest period of time.

Although aerosol therapy is not primarily designed to produce high blood levels, good concentrations can be obtained for two hours following the inhalation of penicillin. A comparison of the total urinary excretion following each of these methods enables us to calculate the portion of the aerosolized penicillin which is actually absorbed from the pulmonary epithelium. We know that no loss of penicillin occurs on endotracheal instillation in the normal anesthetized man. Of 100,000 units administered endotracheally, 15,932 units were excreted in the urine. Only 5.463 units were excreted in the urine when 100,000 units were aerosolized. We can compute the quantity of penicillin actually absorbed from the lung by the simple equation:

$$\frac{100{,}000}{15{,}932} = \frac{x}{5{,}463}$$

x, the quantity absorbed following aerosolization, is found to equal 34,291 units. The average loss within the entire apparatus, obtained by penicillin assay of the rinsings, is 10,225 units or 10.2 per cent. The average loss obtained from assay of the saliva and mouth rinsings during aerosolization is 7,984 units or 8.0 per cent. Thus, the loss sustained before the aerosol reaches the lung is 18,209 units (18.2 per cent). Since 34,291 units are actually absorbed from the lung, the miscellaneous loss, probably mostly into the air, is 47,500 units (47.5 per cent). These various relationships are illustrated in figure 3. Roughly, then about one third of the nebulized

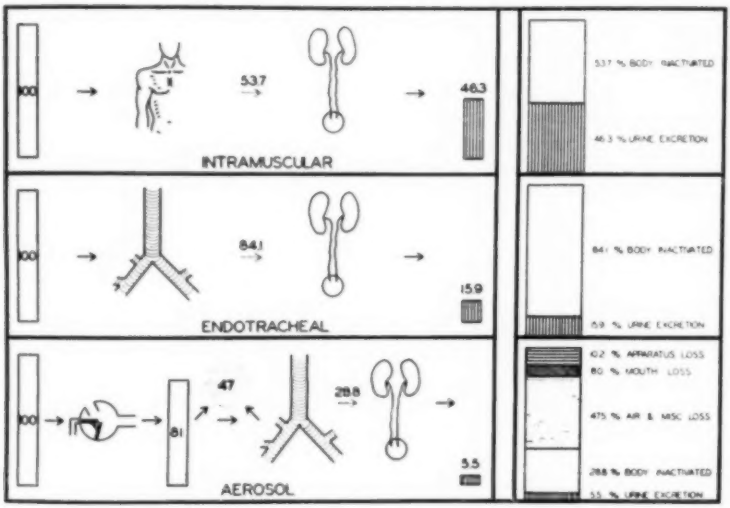

FIG. 3. Schematic representation of the fate of penicillin administered by various routes.

solution is actually absorbed by the lungs, one sixth is lost within the apparatus and the oropharynx and almost one-half is lost into the air.

Summary

1. Intratracheal administration of penicillin in saline solution in normal, anesthetized volunteers revealed that the penicillin molecule is readily absorbed into the blood stream from the alveoli. This absorption is notably slower than that following parenteral administration.

2. Blood levels following intratracheal instillation do not reach the early high peaks seen on intramuscular administration but therapeutically significant blood levels are maintained for twice as long a period of time. The average urinary excretion is 15.9 per cent, or about one third of that following parenteral administration. This suggests that the lung may act as a *depot* from which penicillin may be slowly released.

3. Intratracheal administration is suggested as a practical and advantageous method of therapy under certain, special circumstances.

4. Aerosolized penicillin solution results in early blood levels nearly as high as those obtained by endotracheal administration, but therapeutic levels are maintained for only one third as long a period of time.

5. Following aerosolization, 5.5 per cent of the administered penicillin is excreted into the urine; 10.2 per cent is lost within the apparatus, 8 per cent is lost in the oropharynx and 47.5 per cent is lost on expiration and other losses into the air. Thus one third of the aerosolized penicillin solution actually reaches the lung.

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THE HEREDITY OF GOUT AND ITS RELATIONSHIP TO FAMILIAL HYPERURICEMIA*

By Robert M. Stecher, M.D., F.A.C.P., A. H. Hersh, Ph.D., and Walter M. Solomon, M.D., F.A.C.P., *Cleveland, Ohio*

Despite the fact that gout has long been recognized as a hereditary disease and that much study has been devoted to this phase of the problem, the exact pattern of inheritance has not been clearly identified. It seemed likely that a broader concept of the disease and the application of modern methods of genetic investigation to readily available data might add much to our understanding of the disease. The present study was undertaken in the hope that these potentialities might be realized.

The most striking features of gout have always been associated with the joint phenomena. Characteristically these consist of a series of sudden, acute, painful attacks of arthritis involving with decreasing frequency the joints of a big toe, the feet, the knees and the hands. The joints may become affected overnight and are greatly swollen, very red, markedly tender and hot. There is often fever and leukocytosis. The attacks subside spontaneously in days to months and complete recovery is the rule. Only as a result of repeated attacks and after many years does chronic joint damage with deformity occur. The deposition of uric acid crystals as tophi in the skin about the ears, or in bones about the joints and resulting in punched-out areas seen by roentgen-ray, are the pathognomonic lesions of the disease. They appear only late in the disease, if at all, and they escape detection entirely in many victims. Because the joint manifestations of gout characteristically occur only in middle or later life and because they are often atypical and cannot be correctly identified, many affected members of the gouty family are not recognized and the genetic pattern is rarely complete.

Gouty patients have an abnormally high level of uric acid in the blood, one manifestation of the faulty uric acid metabolism which is characteristic of the disease. Hyperuricemia is present whether the patient is having gouty attacks or not and this abnormality has been observed in patients before they developed clinical gout. A substantial proportion of the near relatives of gouty people have been found to have hyperuricemia. This suggested that the genetic pattern and the mechanism of inheritance of familial hyperuricemia might be recognized and that analysis of this trait could yield valuable information about the heredity of gout. The present study, therefore, is one of the genetics of familial hyperuricemia and for this purpose familial hyperuricemia is considered to have exactly the same significance as clinical gout.

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No attempt will be made to review the literature on the subject. Several recent papers [1, 2] refer to previous statements on the subject. The present study considers idiopathic hyperuricemia as genetically related, if not even identical, with gout. Folin [3] noted idiopathic hyperuricemia in the brother of a gouty patient as did also Jacobson.[4] Talbott [5] studied 136 relatives of 27 gouty patients. He found that 34 of them, or 25 per cent, had serum uric acid levels which were abnormally high. He states that an increased concentration of urate in the body is the most significant factor in gout and that this finding in one fourth of the apparently normal relatives indicates that the manifestation is a familial one which may be present at birth or shortly after. Although the sexes were about evenly divided in the 136 relatives (58 per cent males), of the 34 affected ones, 27, or 80 per cent, were males. Four of the 34 affected relatives were under 20 years of age, the youngest being 14 years. Smyth and Freyberg [6] reported two remarkable gouty families. In one a gouty father and normal mother had three gouty sons and a normal daughter. In the second family the same combination of parents had four normal children but two of the three sons had abnormally high levels of serum uric acid.

The diagnosis of gout in the present series was based upon a summation of clinical and chemical evidence often after observation extending over varying periods of time. Factors considered included the story of typical attacks of gout interrupted by complete remissions for months or years and the finding of hyperuricemia. Punched-out areas in bones and other tophi were found in only a few cases.

In this study, once a patient had been accepted as gouty, it was decided that every one of his tested relatives would be included for consideration and classified as being normal or having familial hyperuricemia. A definite level of serum uric acid demarcation between normal and affected was chosen based upon our experience despite the obvious fact that such an exact distinction would of necessity be arbitrary and that repeated observations on the same individual might fall on different sides of the line.

Certain other well known conditions influencing the level of blood uric acid had to be considered. Hyperuricemia in the absence of gout is sometimes found in kidney insufficiency, lobar pneumonia and leukemia. A high fat diet causes a retention of uric acid with an elevation of its blood level. Blood uric acid can be lowered by proper treatment of gouty patients. Large doses of cinchophen or aspirin were found to reduce blood uric acid drastically.

Although a high level of uric acid in the blood has been recognized as a sign of gout since Garrod [7] announced it in 1848, no definite upper limit of normal or lower limit of gout has ever been established. Jacobson,[4] following a suggestion made years ago by Folin, used serum separated out of clotted blood instead of whole blood for uric acid determination. This procedure proved to be much more reliable than former methods because a sharp line of demarcation was found between normal and gouty individuals in most in-

TABLE I

Serum Uric Acids

1272 determinations on 1,162 individuals

	Number of Individuals	Number of Determinations	Determinations below 6.5 mg.	Determinations 6.5 mg. or over	Average
A. Gouty families					
1. Index cases	41	77	3	74	8.12
2. Hyperuricemia	17	23	1	22	7.37
3. Normal relatives	120	124	123	1	
4. Spouses of gout	23	24	22	2	
Total	201	248	149	99	
B. General population					
5. Normal kidney function	878	927	893	34	
6. Nitrogen retention	83	97	72	25	
Total	961	1,024	965	59	
Grand total	1,162	1,272	1,114	158	

stances, 94 per cent of 177 determinations on 21 gouty subjects being over 7 mg. per 100 c.c. Among 100 non-gouty subjects there were only three determinations above 6 mg.

Because of the importance of recognizing a definite level between hyperuricemia and normal it seemed desirable to determine the dividing line to be used in this study from our own experience of 1,272 tests. These included 248 tests on 41 gouty patients and 159 of their relatives or spouses and 1,024 tests done routinely on 961 patients on the medical wards of Cleveland City Hospital, shown in table 1. All determinations used in this study were made by one individual using Benedict's direct method, and read with a Klett Electric Colorimeter on serum separated from clotted blood. Specimens were collected under oil without regard to fasting.

Table 2 shows the distribution of values in various classes of individuals. Examination of this table shows a natural division of high and low levels

TABLE II

Serum Uric Acid Levels

Distribution of 1,272 determinations

	0–1.9	2.0–2.4	2.5–2.9	3.0–3.4	3.5–3.9	4.0–4.4	4.5–4.9	5.0–5.4	5.5–5.9	6.0–6.4	6.5–6.9	7.0–7.4	7.5–7.9	8.0–8.4	8.5–8.9	9+
A. Gouty families																
1. Index cases									1	2	8	13	14	12	15	12
2. Hyperuricemia										1	7	7	3	3		2
3. Normal relatives			6	11	21	22	16	25	18	4	1					
4. Spouses of gout		1	3	2	2	3	6	2	2	1	1		1			
Total 248		1	9	13	23	25	22	27	21	8	17	20	18	15	15	14
B. General population																
5. Normal kidney function	54	65	106	136	153	162	80	70	42	25	12	5	8	1	2	6
6. Nitrogen retention	2	1	5	7	11	11	12	6	11	6	4	7	3	2	3	6
Total 1,024	56	66	111	143	164	173	92	76	53	31	16	12	11	3	5	12
Grand total 1,272	56	67	120	156	187	198	114	103	74	39	33	32	29	18	20	26

between 6.4 mg. and 6.5 mg. A marked preponderance of determinations in gouty or hyperuricemic individuals fall to the right of this line. A marked preponderance of tests of non-gouty individuals fall to the left of this line. Thus in 77 tests upon 41 patients with gout, all but three are 6.5 mg. or more per 100 c.c. Of 23 determinations on 17 relatives considered to have hyperuricemia, only one was below 6.5 mg. In these two groups of hyperuricemic individuals, uric acid levels were above 6.5 mg. in 96, or 96 per cent of the tests.

Of 1,024 tests on 961 patients on the medical wards, 965 were below the level of 6.5 mg. Of the 59 above this value, 25 were on patients with nitrogen retention, a condition expected to produce hyperuricemia. Thus, only 34 or 3 per cent of the tests showed an unexplained value above 6.5 mg. which might have been due to idiopathic hyperuricemia. As a result of these observations, and in the absence of evidence to the contrary, a serum uric acid level of 6.5 mg., or over per 100 c.c., was tentatively accepted as hyperuricemia or proof of gout.

The validity of this line of distinction between normal and hyperuricemia was tested statistically. A group of 294 normal females of the hospital population gave a mean uric acid level with the standard error of 3.63 ± 0.06 mg. per 100 c.c. with a standard deviation of 1.06 ± 0.04 mg. per 100 c.c. The mean with its standard error for a similar group of 296 normal males was 3.95 ± 0.06 mg. uric acid per 100 c.c. with a standard deviation of 1.15 ± 0.04 mg. per 100 c.c. The difference in the means with its standard error is 0.32 ± 0.08, a significant difference which one could expect as a result of random sampling only about once in more than 15,000 trials. The average uric acid concentration for the males is 1.088 times that for the females, which curiously enough agrees very closely with the differences between the sexes in physical stature as determined many years ago by Galton, and also with the difference in the figure usually taken as the average cranial capacity, 1,200 c.c. for females, 1,300 c.c. for males.

To cut off the normal curve in the plus direction at two times the standard deviation brings the upper level of normality for males to 6.25 mg. and allows about one man in 50 to stand above that level who still might be regarded as normal. If it is desired to reduce this figure to one in 100, then the level of demarcation in round figures could be placed at 6.50 mg., 2.22 times the standard deviation above the mean. A similar estimate for females is 5.98 mg. It is interesting to note that in the sample of 294 normal females there were two who showed 6.0 mg. or more per 100 c.c. These values, 6.5 mg. for males and 6.0 mg. for females, are then taken as the upper levels of normality for purposes of this study.

The present genetic study is based on 44 primary index cases, their 17 hyperuricemic or gouty relatives, and 120 normal relatives. There are also 23 spouses. The group consists of 203 individuals almost equally divided as to sex with 104 males and 99 females. Twelve of the primary index cases had no available relatives and were included only to broaden the ob-

TABLE III
Pedigrees of 40 Gouty Families

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
1. M. A. male (63) 8.0 8.0		(62) 2.9				(39) 4.4 (38) 5.4 (35) 5.9 (31) 5.9 (27) 4.9 (23) 5.1	(40) 3.9
2. C. B. male (65) 10.8 9.5				(70) 5.2			
3. J. B. male (50) 6.5			(72) 4.2		(41) 2.6		
4. G. C. male (62) 7.8 7.2 7.8 7.3		(58) 5.6				(36) 5.2	(28) 4.6
5. E. C. male (61) 7.6 8.1					(64) 3.7 (62) 4.3 (60) 3.7 (56) 5.1		(38) 5.1
6. D. D. male (70) 8.4 8.8						(48) 4.1 (38) 4.6 (32) 5.8 (25) 7.2	(36) 5.4
7. L. D. male (48) 7.3				(66) 5.4	(51) 7.1		
	8. B. B. female (51) 7.1	(45) 6.0				(12) 4.8	(30) 3.7 (28) 4.8 (26) 4.1 (25) 4.7 (24) 4.5 (22) 4.8 (19) 4.8 (16) 4.3
9. F. D. male (46) 7.0 5.5			(74) 4.4				

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
10. H. D. male (50)			(68) 5.4		(52) 6.6	(23) 5.0	
11. H. D. male (50) 7.3			(82) 4.9	(55) 4.1 (44) 5.4 (38) 4.3	(61) 3.5 (58) 4.7 (46) 4.4		
12. G. F. male (71) 6.9 8.0					(68) 8.2		
	13. Mrs. W. female (68) 6.1 6.6 8.2	(70) 5.0				(44) 6.3 (31) 6.8	(47) 5.5
14. D. H. male (61)		(68) 4.6		(69) 5.9		(40) 6.5 (38) 5.4 (34) 4.3	(38) 3.4 (31) 5.1 (30) 4.3 (28) 3.4
15. J. H. male (52) 7.1 9.0		(50) 6.9 7.7	(72) 5.1	(40) 7.4			(27) 2.7 (25) 4.3 (21) 3.9 (18) 3.9
	16. G. H. male (40) 7.2 7.4	(40) 2.4					(12) 2.6 (10) 3.6
17. P. J. male (50) 8.5 9.8		(49) 3.8				(16) 5.4	
18. J. K. male (49) 8.3		(47) 4.5			(63) 5.4 (47) 3.5	(12) 4.5	(27) 3.8 (23) 3.2 (19) 4.3
19. S. K. male (27) 7.3			(49) 2.8	(18) 5.5	(11) 3.3		
20. T. K. male (67) 8.3 7.6 7.5 7.5		(63) 4.8		(75) 3.7 (60) 5.8			(45) 4.2 (41) 3.4

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
21. O. K. male (53) 8.9		(55) 4.6		(61) 6.1		(14) 4.0	(32) 4.4
22. E. L. male (50) 9.2		(48) 5.2	(81) 4.8	(52) 5.3		(19) 5.7	(17) 4.9
23. A. L. male (62) 8.5 9.2 8.5				(48) 7.5			
24. O. L. male (68) 7.2 8.1		(66) 3.3					(39) 3.0 (34) 3.6
25. S. N. male (43) 6.6 6.3		(40) 2.9	(65) 4.5	(37) 5.6			(13) 4.4
26. J. P. male (58) 7.3 8.4 8.7 10.7			(80) 9.4 8.3	(55) 3.4 (44) 3.4	(49) 3.9 (42) 2.8		
27. J. P. male (66) 7.7 7.2 9.0 7.6				(70) 6.1 (65) 5.6		(42) 5.5 (35) 5.8	(41) 3.7
28. E. S. male (46) 8.5		(44) 4.8	(69) 9.3	(45) 7.0		(19) 5.7	(16) 4.7
	29. Mrs. S. female (69) 6.7 9.3				(71) 6.9 (65) 7.1		
	30. Mrs. B. female (65) 7.1	(80) 4.5				(45) 7.6 (40) 8.1 (38) 5.2	
	31. Mrs. B. female (71) 6.9						(48) 5.3 (31) 5.2

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
	32. R. B. male (40) 8.1	(38) 3.8				(20) 3.9	
	33. F. B. male (45) 7.6	(42) 2.8				(18) 3.9	(20) 2.9
34. S. S. male (48)		(50) 4.1					(32) 4.0 (30) 5.0 (27) 3.9 (24) 3.1
35. H. S. male (30) 8.7 7.6 8.0				(33) 7.8 (27) 5.3	(13) 3.5		
36. J. V. male (48) 8.1		(40 4.2)			(44) 3.1		(28) 3.5
37. J. V. male (64) 8.1 8.5						(34) 4.1	
38. G. W. male (46) 9.5		(45) 5.6				(28) 6.7	(28) 4.4 (24) 3.8
39. M. W. male (32) 8.8 6.2			(62) 5.5	(30) 5.1 (26) 5.9	(38) 3.1 (34) 3.4 (22) 4.2 (20) 3.8		
40. S. W. male (61) 7.0						(28) 5.1	

One father of an index case was seen in family No. 15, (82) 4.1, 2.7. Twelve additional index cases (those without relatives) were as follows: (73) 6.9; (72) 8.7; (56) 8.7; 7.1, 7.8, 6.6; (44) 7.4; (70) 6.9; (61) 8.6, 11.2, 7.7, 7.6; (65) 8.8; (61) 7.6, 9.4; (53) 6.5; (43) 9.1; (51) 6.9; and (58) 8.5.

servations on serum uric acid levels of gouty people. There are thus 32 primary gouty families. Eight of the 16 hyperuricemic or gouty relatives were made secondary index cases in order to include their children in the study. There is then a total of 52 index cases, 40 of which serve as starting points for the study of groups of relatives. Full data of the 40 families are

presented in table 3. This shows the age when seen and sex of each index case, the age, sex and relationships of each relative examined and all of the serum uric acid determinations done on the entire group in the course of this study. The spouses are included so that the reader may reconstruct the pedigrees if he wishes. Each secondary index case is a duplication having been shown before in a previous family. Initials are given only for index cases. The relationship is shown by the column, age is given in brackets. The relatives we have considered affected are indicated by underlining.

Of the 44 primary index cases, all had gout, all were male, all had high serum uric acid levels, save three men with undoubted gout, known to have had a high level of whole blood uric acid but who died before this study was started, and whose families were known and available to us. Seventy-seven serum uric acid determinations on these 41 index cases averaged 8.12 mg. per cent. The lowest determinations were 5.5, 6.2 and 6.3 mg. per cent, these three being all that fell below 6.5 mg. each in an individual who had other determinations above this level.

TABLE IV

Hyperuricemia in Relatives

	Mother	Brother	Sister	Son	Daughter
Number examined	11	23	24	33	45
Number affected	2	4	5	5	0
Proportion affected (%)	18	17	21	15	0

Having the above data available, it seemed desirable to investigate the proportions of involvement among different degrees of relationship. The results are shown in table 4. Because of the known preponderance of gout in males it seems desirable to consider each sex separately. Inquiry was made concerning all the parents. Of 88 parents of 44 primary index cases only 12 were available for examination. These included the mother in 11 families. Twice she was found to have hyperuricemia but never gout. One father (of the index case J. H., family No. 15) examined was thought to have gout clinically but he showed a normal uric acid level twice. One other father was reported to have had gout but he has not been included in our computations. Thus 2 of 12 parents or about 17 per cent of those examined were found to have hyperuricemia. No attempt was made to analyze involvement of parents of the hyperuricemic relatives because they had one involved parent by definition.

Of the primary index cases, 16 had brothers. These 16 men had 23 brothers of whom 4 or 17 per cent had hyperuricemia. Twelve primary index cases had 22 sisters. One other person, the mother of an index case, had hyperuricemia and her 2 sisters had hyperuricemia, one of them gout. Of 24 sisters then, 5 or 21 per cent had hyperuricemia. The incidence of hyperuricemia in the siblings of gouty people is about 20 per cent and there is no significant sex difference.

TABLE V

Classification According to Parents

Family	Father	Mother	Total Sons	Affected Sons	Total Daughters
Both Parents Affected					
15	Gout	H.U.A.	0	0	4
Father Affected					
6	Gout	Unknown	4	1	1
38	Gout	Normal	1	1	2
1	Gout	Normal	6	0	1
14	Gout	Normal	3	1	4
27	Gout	Unknown	2	0	1
18	Gout	Normal	1	0	3
4	Gout	Normal	1	0	1
21	Gout	Normal	1	0	1
22	Gout	Normal	1	0	1
28	Gout	Normal	1	0	1
32	H.U.A.	Normal	1	0	0
33	H.U.A.	Normal	1	0	1
10	Gout	Unknown	1	0	0
17	Gout	Normal	1	0	0
37	Gout	Unknown	1	0	0
40	Gout	Unknown	1	0	0
34	Gout	Normal	0	0	4
24	Gout	Normal	0	0	2
20	Gout	Normal	0	0	2
36	Gout	Normal	0	0	1
25	Gout	Normal	0	0	1
5	Gout	Unknown	0	0	1
16	H.U.A.	Normal	0	0	2
Mother Affected					
8	Normal	H.U.A.	1	0	8
29	Unknown	H.U.A.	2	2	0
30	Normal	H.U.A.	3	2	0
26	Unknown	H.U.A.	3	1	2
13	Normal	H.U.A.	2	1	1
31	Unknown	H.U.A.	0	0	2
Both Parents Normal					
15*	Normal	Normal	2	2	0
			40	11	48

* Refers to parents of index case.

Thirty-three sons from 19 families were studied. The father was the index case 16 times, 14 times because he had gout, twice because he had hyperuricemia. The mother was the index case 3 times, once with gout, twice with hyperuricemia. Of 33 sons, 5 or 15 per cent had hyperuricemia. Of 45 daughters, not one was found affected. These 45 daughters came from 22 families. The father was the index case 19 times, the mother three

times. Seventeen of the fathers had gout, two had hyperuricemia. All the mothers had hyperuricemia.

Study of table 5 shows the proportion of involved offspring from various combinations of involved and normal parents. In only one family, No. 15, were both parents involved, the father with gout, the mother with hyperuricemia. The four daughters from this union were normal. There were no sons. In nine families sons were born of gouty fathers and normal mothers (Nos. 38, 1, 14, 18, 4, 21, 22, 28, 17). In two other families the father had hyperuricemia without gout, the mother was normal (Nos. 32, 33). These families had 18 sons and 16 daughters. In only one family of this known combination was an affected son produced (No. 38). In five other families with gouty fathers, but mothers unknown (Nos. 6, 27, 10, 37, and 40), there were nine sons and two daughters with only one son affected (No. 6). There were six families with mothers with hyperuricemia and three normal fathers (Nos. 8, 30, 13) and three fathers untested (Nos. 28, 26, 31). In family 26 reference is to parents of the index case. There were 11 sons in these families of whom six were affected. Four of these families had daughters (Nos. 8, 26, 13, 31), a total of 13, all normal. Both parents of index case No. 15 were normal and both sons, their only children, were affected. In eight other families, the mothers were normal and fathers unknown (Nos. 39, 3, 9, 10, 11, 19, 22, and 25). These eight families will not be discussed because the possibilities of an affected father cannot be excluded.

In six families with gouty fathers (Nos. 34, 24, 20, 36, 25, 5) and another family with hyperuricemic father (No. 16) and the mothers normal or unknown, there was a total of 13 daughters, all normal, but no sons.

It is seen that in every instance where something was known about at least one parent, not a single affected daughter among 48 was found although there were 10 affected of 40 sons. Furthermore, the degree of involvement in the parents was no reliable index as to how they would transmit the abnormality. Two affected parents had only four daughters, all unaffected. Two normal parents with only two sons had both affected. Of 23 families with the father involved but mother normal or unknown there was a total of 27 sons, of whom only one each in two different families was affected. There were 31 daughters in these families, only three of whom were in the two families with affected sons. There were six families with affected mothers and normal or unknown fathers. These families produced 11 sons of whom six were affected. Four of these six families produced affected sons. These four families with six affected sons produced only three daughters. Thus with the father affected, only two of 27, or 8 per cent of the sons were affected. With mothers affected, six of 11, or one-half of the sons were affected. The effect of sex was marked. The apparent immunity of daughters is not so convincing when we realize that only 6 of 21 families having sons and with one parent involved proved that they could transmit hyperuricemia to a son. Six daughters only sprang from these six

families compared to 15 sons, eight of whom were affected. Forty-two daughters sprang from 23 families which demonstrated no ability to transmit hyperuricemia.

Table 6 is a study of sibships. The constitution of the parents is given when known. This may seem like a duplication of the previous table but the classification is according to involvement or not of a sibling. It includes all of the sibships in the previous table, as well as others in which nothing

TABLE VI

Classification of Families According to Sibships

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Brothers						
15	2	2	0	0	Normal	Normal
28	2	2	0	0	Unknown	H.U.A.
30	3	2	0	0	Normal	H.U.A.
26	3	1	2	0	Unknown	H.U.A.
13	2	1	1	0	Normal	H.U.A.
39	3	1	4	0	Unknown	Normal
6	4	1	1	0	Gout	Unknown
38	1	1	2	0	Gout	Normal
3	1	1	1	0		
5	1	1	4	0		
10	1	1	1	1		
12	1	1	1	1		
18	1	1	2	0		
36	1	1	1	0		
35	3	2	1	0		
7	2	1	1	1		
19	2	1	1	0		
21	2	1	0	0		
23	2	2	0	0		
25	2	1	0	0		
22	2	1	0	0		
20	3	1	0	0		
27	3	1	0	0		
11	4	1	3	0		
Sibships with Normal Brothers						
1	6	0	1	0	Gout	Normal
14	3	0	4	0	Gout	Normal
27	2	0	1	0	Gout	Unknown
8	1	0	8	0	H.U.A.	Normal
18	1	0	3	0	Gout	Normal
4	1	0	1	0	Gout	Normal
21	1	0	1	0	Gout	Normal
22	1	0	2	0	Gout	Normal
28	1	0	1	0	Gout	Normal
32	1	0	0	0	H.U.A.	Normal
33	1	0	1	0	H.U.A.	Normal
10	1	0	0	0	Gout	Unknown
17	1	0	0	0	Gout	Unknown
37	1	0	0	0	Gout	Unknown
40	1	0	0	0	Gout	Unknown

TABLE VI—*Continued*

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Sisters						
29	0	0	3	3	Unknown	Unknown
10*	1	1	1	1	Unknown	Unknown
12*	1	1	1	1	Unknown	Unknown
7*	2	1	1	1	Unknown	Unknown
Sibships with Unaffected Sisters Only						
15			4	0	Gout	H.U.A.
34			4	0	Gout	Normal
24			2	0	Gout	Normal
16			2	0	H.U.A.	Normal
36			1	0	Gout	Normal
25			1	0	Gout	Normal
5			1	0	Gout	Unknown
31			2	0	H.U.A.	Unknown

* Shown in table of Affected Sons.

is known of the parents. According to table 5, there were 24 sibships with at least one affected brother. In eight of these the constitution of one or both parents is known. These 24 sibships had 51 males of whom 29 or 57 per cent were affected. Of the 24 families 15 or 62 per cent had daughters, 26 in number, of whom one each in three sibships was affected (Nos. 10, 12, 7). Another 15 sibships had 23 males, all normal. Each of these families had an affected parent or it would not have been included in the study. Ten of the sibships had 23 females, all normal. Four families had affected sisters, three mentioned above (Nos. 10, 12, 7) and another (29) with three sisters all involved. Eight additional sibships without sons had 17 daughters, all normal.

Involvement of women with hyperuricemia was rare but significant. Of the four sibships with involved women, a total of six women were examined and all found involved. Of four brothers of these women, three were found affected. Nine of the 10 people in these four sibships involving affected women were affected. Only two other affected females were discovered in the entire study, a spouse (No. 15) and a mother (No. 26). Of the eight women with hyperuricemia, only one could possibly be considered to have clinical gout.

Consideration of the data of table 3 and table 5 is sufficient to show that the inheritance of hyperuricemia exhibits certain irregularities. This is emphasized more clearly by an examination of the pedigrees of several of the more significant families. Figure 1 shows in pedigree form the data for families 15 and 16, while figure 2 gives the pedigree for the related families 28, 29, 30, 31, 32 and 33 of table 3.

In figure 1, neither parent in generation I has hyperuricemia, but both sons show the trait. This in itself would be an indication that the trait is a recessive and that the parents are both heterozygotes. But in the same pedigree in generation II the first set of parents both show the trait but their four daughters are not affected. Obviously, if the trait were a simple autosomal recessive all these daughters should show the trait. Gout in women is known to be rare. In the entire study 62 individuals showed hyperuricemia of whom only eight were women. Of the affected group, 13 per cent were women and 87 per cent were men. Because of the fact that seven times as many men as women are affected, this pedigree might be satisfactorily regarded as that of a recessive in which there was considerable lack of penetrance in the female.

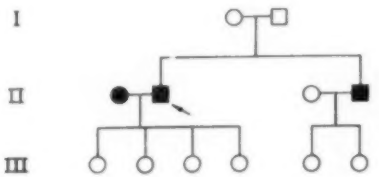

FIG. 1.

In figure 2 we have a remarkable family of three affected sisters. The family of the oldest sister consists of two normal daughters; the second sister has two sons, both affected; the third sister has three sons, two of whom are affected. This pedigree has the appearance of a typical dominant. If it were recessive, both parents of the three sisters and the husbands of the two younger sisters would need to be heterozygotes and so would the spouses of all of the gouty people who begot affected children. Because of the low incidence of hyperuricemia in the population, the probability of this seems to be very slight. It is more probable that the spouses were homozygous for a normal recessive gene and the sisters themselves as well as other gouty

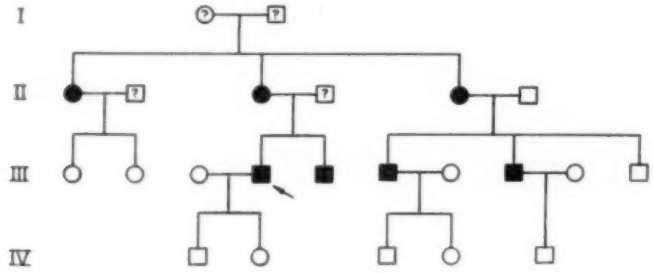

FIG. 2.

parents with affected offspring were heterozygous for a dominant gene which acts irregularly in many families. It is clear that a dominant gene which lacks penetrance can resemble a recessive in some pedigrees.

These two pedigrees, taken in conjunction with the other families of table 3, justify the conclusion that the genetic peculiarities of hyperuricemia are mainly the expression of an autosomal dominant gene which lacks penetrance in both sexes, but with a much lower penetrance in the female than in the male, perhaps about one-seventh as much.

Gout is a disease in which the average age of recognition is in the middle or later life and the lack of penetrance observed might be dependent upon the low age of the population studied. The relationship of age to serum uric acid level was tested by computing the coefficient of correlation (r). The determination was made for each sex separately. The value of r with its standard error was found to be $+ 0.088 \pm 0.129$ for male relatives of gouty people. This shows complete lack of correlation indicating that there is no significant increase of the serum uric acid in males after the age of 20. No alteration in penetrance is to be expected with advancing years. The finding in regard to women is quite different. Here r was found to be $+ 0.44 \pm 0.09$, a degree of correlation which is definitely significant. A marked difference is thus revealed between men and women. Inspection of the correlation table shows that every woman with hyperuricemia was over 50 years of age, a fact which suggests that normal menstrual function inhibits the development of idiopathic hyperuricemia.

Whether the level of serum uric acid is definitely established for men at adolescence or earlier in childhood is at present unknown. The present series included only eight males below the age of 20, so that our observation on this point is limited. Talbott, however, observed hyperuricemia in four males under the age of 20, the youngest being 14. His observations differed from ours also regarding the age of females. Among the relatives of gouty patients, he records seven hyperuricemic women all under the age of 42, the youngest being 21.

From the above considerations we tentatively conclude that hyperuricemia is an autosomal dominant with low penetrance in both sexes, but considerably lower in the female than in the male. Since it is desirable wherever possible to put the conclusion to the numerical test, even when the data for making such a test may be somewhat inadequate and inconclusive, we have assembled the pertinent data from table 3 in table 7. It is well known that in analyzing human genetic data a correction must be made for small family size. When families are small, certain families of the proper genetic constitution but having several unaffected offspring will go unrecognized and therefore uncounted. The observed affected offspring will consequently be more than the theoretically expected number.

Hogben [8] has published tables of corrective factors for families of different size. These tables are for testing ratios in fraternities for genes with

full penetrance. The test in table 7 is for males only. The fraternities used from table 3 are those with more than one son, and in which at least one son was affected. The test is made for a 1:1 ratio, since if one son is affected it follows that one parent was at least heterozygous for the dominant gene with the other parent homozygous for the normal recessive allele. Because of the low incidence of hyperuricemia in the population there are not likely to be many homozygous dominants or matings where both parents are heterozygous. Twenty fraternities with more than one son and with at least one son affected are available (families 2, 6, 7, 11, 13, 15, 19, 20, 21, 22, 23, 25, 26, 27, 28, 30, 35 and 39 with one sibship, 14 with 2). In these 20 fraternities there are 51 men, 26 of whom are affected. After correction for small family size the number expected with its standard error is 30.9 ± 2.7. This shows a remarkably good agreement considering the lack of full penetrance. In fact, if the provisional conclusion that hyperuricemia is an autosomal dominant with lack of full penetrance be accepted, then the results may be used to estimate the penetrance. That is, 26 are observed affected where 31 are expected, showing that on this basis penetrance of the gene is about 84 per cent in heterozygous males. Although the 203 individuals in the study series were equally divided as to sex, there were 54 hyperuricemic males compared to eight hyperuricemic females, a ratio of 7 to 1. Penetrance in women therefore seems to be about one-seventh as high as in men or about 14 per cent.

TABLE VII

Comparison of Affected Men with Theoretical Expectancy on Basis of 1:1 Ratio. Corrected for Family Size

Number of Siblings	Number of Families	Total Number of Men	Affected Men	Factor	Expected Affected
2	11	22	15	1.333	14.663
3	7	21	9	1.715	12.005
4	2	8	2	2.134	4.268
	20	51	26		30.936

When the mother is the parent affected, there seems to be a stabilizing effect on the action of the gene so that penetrance in the sons seems to be almost complete. Of six sons born of affected mothers, three had hyperuricemia compared to 27 sons of affected fathers, only three of whom had hyperuricemia. Although the sample is small, it appears that the higher penetrance in sons of affected mothers may be due to a maternal effect, some influence on the cytoplasm of the egg at the time of maturation, or during the uterine history.

In conditions occurring predominantly in males the possibility of sex linkage is always suggested. In sex linkage the gene for the suspected trait is carried on the X chromosome which males inherit from their mother.

With mothers affected all sons become involved. Fathers do not transmit to their sons. This situation is approached in this series in that six of eight sons of five affected mothers had gout. Fathers, however, do not transmit sex-linked characters to their sons but only produce carriers of their daughters. In this series three fathers transmitted gout to their sons, table 3, Nos. 7, 14, 38. Smyth and Freyberg [6] described two similar instances. The data do not support the theory that gout or hyperuricemia are sex-linked characters.

The possibility that hyperuricemia might be a recessive trait was tested in the following way: When one parent shows a trait and some of the children are affected, the other parent may be normal if the trait is dominant. If the trait be recessive, however, the phenotypically normal parent must be heterozygous or affected children will not appear. It is obvious that there must be a sufficient reservoir of heterozygotes in the population to give a reasonable probability that the required number of matings may occur with random mating. In other words the genetic analysis of the data of the pedigrees must be consistent with the gene frequencies in the population.

Since about one-eighth of the relatives of gouty people were found to have unsuspected hyperuricemia it seemed reasonable to suppose that this trait might be observed in a discoverable proportion of the general population selected at random. In an effort to test this supposition, routine serum uric acids were done on patients on the medical wards at City Hospital, care being taken only to exclude known gout. Of 1,024 determinations on 961 patients, only 59 or 5.7 per cent were over 6.4 mg. per 100 c.c. Those included 25 tests on patients with urea nitrogen retention, 16 with cardiac failure, eight malignant growths or leukemia, two pneumonia, four anemia or recent hemorrhage, and three, all below 6.8 mg., who subsequently had lower values and were considered normal. Only one patient, a diabetic, had a level of 9.1 mg. per 100 c.c., the only one of 961 individuals tested who might be considered to have constitutional hyperuricemia. This result was sufficient to discourage further attempts to discover the true incidence of constitutional hyperuricemia in the general population by this method.

Despite the obvious inadequacy of these data they were used tentatively as a basis for gene frequency analysis. Instead of using 1 in 1,000 for the proportion of hyperuricemia in the general population this figure was arbitrarily adjusted to 3 in 1,000 in order to be conservative in the conclusions. This assumption weights the argument strongly in favor of the theory that hyperuricemia is inherited as a recessive. Despite this advantage the theory earns little support in the following argument.

With hereditary characters the frequencies of homozygous dominants, heterozygotes, and homozygous recessives in a population mating at random agree with the equation $d^2 + 2dr + r^2 = 1$, where d (the frequency of the dominant gene) $+ r$ (the frequency of the recessive allele) $= 1$. If the incidence in the population is assumed to be 3 per 1,000, and the gene for the trait is dominant, $d = 0.0017$, $r = 0.9983$ and the corresponding frequencies

for d^2, $2dr$ and $2r^2$ are 0.000 +, 0.003 — and 0.997 respectively. If the gene for the trait is recessive, $d = 0.9453$ and $r = 0.0547$ and genotypic frequencies are 0.894, 0.103 and 0.003 respectively. If hyperuricemia were a recessive, under these circumstances a gouty person would have one chance in 10 of choosing a mate who was heterozygous for the condition. As a recessive, gout could be transmitted by a gouty parent only if his spouse were heterozygous. Of 16 families of gouty fathers which produced sons (table 4) only three had affected sons indicating that the mothers were heterozygous. Since 12 of these families had only one son it seems likely that one or two other mothers also must have been heterozygous. Of six affected mothers, four had affected sons. It appears then that about 8 of 22 spouses would have been heterozygous. Of six affected mothers, four had affected sons. It appears then that about eight of 22 spouses would have been heterozygous, an incidence of about 1 in 3. The production of heterozygotes in one third of the population would require an incidence of homozygotes of about 3 per cent, a figure certainly much too high for hyperuricemia as we found it, and at great variance from the figure of 0.003 which was liberally assigned to it as a result of the survey of the general population.

In view of the fact that the most favorable interpretation possible of these very meager data leads to conclusions which in no way support the theory that hyperuricemia is a recessive trait, this supposition was abandoned. All of the phenomena observed seem to be adequately explained by assuming that hyperuricemia is inherited as a single autosomal dominant trait with incomplete penetrance.

The relationship between clinical gout and hyperuricemia is not completely clear. Hyperuricemia is inherited. It has been observed before puberty by Talbott.[5] There is reason to believe that the incidence of hyperuricemia in the population and the severity of hyperuricemia in the individual remain unchanged with advancing age. Gout, on the other hand is a disease of middle or late life, the incidence of which definitely increases as age advances.[9, 10] The occurrence of gout seems to be determined by environmental factors acting upon genetically susceptible people, those with hyperuricemia.

It is commonly thought by lay people that gout can be induced by overindulgence and dietary indiscretions. Excessive intake of purine foods, malt liquors, and fats are known to cause an increase in the level of blood uric acid and to induce attacks of gout in susceptible individuals. Gout developed in G. H., secondary index, case No. 16, after this study was completed. Talbott [5] also has seen gout develop in people known to have hyperuricemia. Perhaps nothing will induce gout in non-susceptible individuals. Abnormally high levels of blood uric acid of themselves are not enough to guarantee attacks of gout. Patients with uremia, leukemia, polycythemia, pneumonia, malignancy, cardiac failure, and hemorrhage often develop hyperuricemia as high or higher than is seen in gout, without developing joint symptoms or tophi. Gout is dependent upon unknown factors in addi-

tion to high uric acid concentrates in the blood. These factors still remain unidentified despite intensive investigation for many years.

Summary

This study is based on 248 serum uric acid determinations on the 201 members of 44 gouty families as well as 1,024 serum uric acids on 961 patients examined routinely at City Hospital. A clear-cut division between hyperuricemia and normal was recognized clinically at 6.5 mg. per 100 c.c., which was confirmed by statistical analysis. The incidence of hyperuricemia in the relatives of gouty patients was found to be 18 per cent among 11 mothers, 17 per cent among 24 brothers, 21 per cent among 24 sisters and 15 per cent among 33 sons. Not a single daughter among 45 tested was found to have hyperuricemia.

There was no correlation between age and hyperuricemia among male relatives of gouty patients, but a significant correlation was found among female relatives. Since no female relative in this series was affected below the age of 50, it seems possible that normal menstrual function inhibits hyperuricemia.

On the assumption that gout and the hyperuricemia found in some of the relatives of gouty patients are the expression of the same genotype both in the same family and in different families, this series was developed in an attempt to detect the genetic mechanism involved. The genetic peculiarities of hyperuricemia are such that in some families it resembles an autosomal recessive, whereas in others it is more like an autosomal dominant. These peculiarities are, however, quite satisfactorily explained if the gene involved is an autosomal dominant which lacks penetrance in both sexes, but has a much lower penetrance in the female than in the male. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male, about 12 per cent or less in the female. This conclusion brings the data of the pedigrees in good agreement with a tentative estimate of the gene frequencies in the general population.

Note: Since this article was submitted for publication, three studies have appeared which are pertinent to the subject: Smyth, C. J., Cotterman, C. W., and Freyberg, R. H., Jr.: The genetics of gout and hyperuricemia—an analysis of 19 families, Jr. Clin. Invest., 1948, xxvii, 749–759; Smyth, C. J., Stecher, R. M., and Wolfson, W. Q.: Genetic and endocrine determinants of the plasma urate level, Science, 1948, cviii, 514–515; Hellman, L.: Production of acute gouty arthritis by adrenocorticotropin, Science, 1949, cix, 280–281.

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THE USE OF CURARE (D-TUBOCURARINE IN OIL AND WAX) IN THE TREATMENT OF MUSCLE SPASM IN RHEUMATIC DISORDERS *

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The present report records our preliminary observations in a consecutive series of 58 cases of various types of rheumatic disease in which treatment with curare in oil and wax was instituted. Curare was administered in 51 cases in which muscle spasm actually existed. The remaining seven cases were those in which a diagnosis of psychogenic rheumatism was made. In these, subjective symptoms of "muscle stiffness" without objectively demonstrable spasm were prominent along with many other bizarre musculoskeletal symptoms. Curare was used in this group primarily for control purposes, as an aid in evaluation of results in the larger group. Although the number of patients studied is not large, the results have been definitive. The conclusions to be drawn with regard to the effectiveness of the drug in the various syndromes studied are unmistakable. This preliminary report may indicate not only the area of usefulness of the drug, as revealed by our experience, but may encourage further interest in its study in other, related types of rheumatic disease.

The historical background of the use of curare, the pharmacologic properties of which were first demonstrated by Claude Bernard as far back as 1850, and its physiologic properties, as well as its more recent applications have been well described in a series of publications by Schlesinger and Ragan.[1, 2, 3, 4, 5]

Briefly, tubocurarine is a quarternary ammonium salt. These salts, as a group, possess the property of paralyzing conduction at the myoneural junction. In certain concentrations, tubocurarine has an almost pure myoneural junction effect. This neuromuscular block can be employed therapeutically, because with certain specific concentrations of curare as employed in the present study, involuntary muscle spasm is abolished, whereas voluntary muscular contraction is entirely unaffected.

The effect of curare in creating myoneural block has been known for many years. Practical application of this knowledge was not possible, however, until recently, when a crystalline derivative of the crude alkaloid, with predictable pharmacologic properties and toxicity became available. The earlier aqueous preparations of curare were not well suited to the treatment

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of muscle spasm associated with syndromes of a chronic nature. Because of their rapid elimination their action was evanescent, and because of rapid absorption, aqueous preparations produced high concentrations of the drug, which may induce severe toxic side effects.

The preparation we have employed consists of a suspension of 3 per cent of d-tubocurarine chloride in 4.8 per cent wax and peanut oil. This suspension is given by intragluteal injection, yielding a slow acting effect, generally lasting from 24 to 48 hours, and in some instances more than 72 hours. With such dosage the desired clinical response may be elicited without serious reactions. Milder side effects, which will be described later, have occurred in some cases. As Schlesinger has shown in reports on his very extensive clinical experience with this drug, it is neither toxic, nor habit forming. Nor is there evidence that tolerance to the drug develops.[3]

When a suspension of d-tubocurarine chloride in wax and peanut oil became available [1, 2, 3] we became interested in the therapeutic value of this drug in the treatment of muscle spasm associated with a variety of rheumatic disorders. We realized, of course, that the basic pathologic process respon-

TABLE I

Diagnosis	Number of Cases	Definitely Beneficial	Not Beneficial	Questionably Beneficial
Rheumatoid arthritis	23	0	18	5
Periarthritis of shoulder	5	5	0	
Low back pain	13	7	4	2
Osteoarthritis with associated periarticular fibrositis	6	0	4	2
Fibromyositis	4	0	4	0
Psychogenic rheumatism	7	0	7	0

sible for the muscle spasm would require treatment. Nevertheless, we felt that resolution of the associated muscle spasm, if possible, might aid in functional rehabilitation at the earliest time. Protective splinting by muscle spasm may serve a useful purpose by preventing further irritation of the underlying pathologic lesion in the joint or bursa, but such spasm has its deleterious aspects. If a state of continuous spasm is allowed to persist muscles may undergo fixed contracture. Atrophy of the opposing extensor groups of muscles is likely to occur, and in certain inflammatory states such as rheumatoid arthritis, subacromial bursitis, and periarthritis of the shoulder, adhesive inflammatory changes may supervene with limitation of mobility requiring manipulative procedures for restoration of normal joint function.

The clinical evaluation of d-tubocurarine chloride in oil and wax suspension is based on study of cases in the following categories: (1) rheumatoid arthritis, (2) periarthritis of the shoulder, (3) low back pain, (4) osteoarthritis with associated periarticular fibrositis, (5) fibromyositis, (6) psychogenic rheumatism (table 1).

The results were recorded as either definitely beneficial; not beneficial; questionably beneficial.

Results were tabulated as definitely beneficial only when striking relief of symptoms occurred with curarization (estimated at an average of 85 per cent). These findings were confirmed by objective examination.

Results were tabulated as questionable when the patient reported slight subjective improvement which could not be confirmed by objective examination. In many instances it was felt that subjective change could not be directly attributed to curarization.

Analysis of Results

Rheumatoid Arthritis. There were 23 cases of generalized rheumatoid arthritis. The duration of the disease varied from one to 20 years, the majority of the patients (16 cases) having been ill for over five years. All presented typical clinical and roentgenographic evidence of rheumatoid arthritis; all were in a stage of activity as indicated clinically and by rapid sedimentation rates, and many of them showed characteristic deformities. These patients received three to six injections of 175 units (1.0 c.c.) of curare in wax and peanut oil every two to three days; this treatment was continued with one patient for a period of six weeks. In several instances reactions without relief of muscle spasm were noted following injection. In these cases administration of the drug was discontinued.

In none of these patients was there clinical evidence of definite improvement, either subjective or objective. In five cases there was questionable subjective improvement which could not be confirmed by examination. It is perhaps significant that of these five, one was suffering from Marie-Strumpell (rheumatoid) spondylitis and four presented evidence of Marie-Strumpell spondylitis associated with rheumatoid arthritis of peripheral joints. Three cases of typical rheumatoid spondylitis, however, were not benefited either subjectively or objectively.

Periarthritis of Shoulder. There were five cases of periarthritis of the shoulder. The roentgenograms in all were normal.

These patients presented the characteristic symptoms of pain in the shoulder and along the course of the deltoid muscle, pain always increased by attempts at abduction, external or internal rotation of the arm. In all cases normal range of motion was to some degree restricted. Definite adhesive changes limiting the range of mobility were associated in two. In these, manipulation of the shoulder under anesthesia was performed. In the other three cases restriction in the range of motion was caused entirely by muscle spasm. In one of these, manipulation of the shoulder was performed in the course of tonsillectomy, but no adhesions were present.

In all five cases of periarthritis of the shoulder there was distinct improvement, both subjectively and objectively, attributable to the administration of curare. In the two cases in which manipulation was performed to break

up adhesions, subsequent administration of curare along with the usual physiotherapeutic measures was of definite benefit in relieving muscle spasm and thus increasing the range of motion.

These patients were generally given 1.0 c.c. of curare every other day during the stage of most severe muscle spasm. Following improvement 1.0 c.c. was given weekly during the course of follow-up treatment until the normal range of motion was restored. These patients all received, in addition, physiotherapy, including infra-red heat, massage, and active exercises with or without assistance, depending upon the need or capacity of the patient. The results immediately following each injection of curare were so striking, however, that there can be no question of the effect of the drug in this condition. With relief of muscle spasm, less analgesia was required and active exercises were carried out more easily, less painfully. The result was acceleration in the restoration of the normal range of joint function.

Low Back Pain. There were 13 patients with low back pain resulting from varying causes. In seven of these cases, prompt and striking objective and subjective improvement followed the administration of curare; in four, the drug had no effect; in two, improvement following curare was questionable.

Of the 13 patients in this group, two with acute traumatic low back sprain were completely relieved of muscle spasm and of subjective symptoms by a single injection of 1.0 c.c. of curare in oil and wax. In one, roentgenograms of the lower back were negative; in the other, the acute sprain was superimposed upon a chronic, degenerated lumbar intervertebral disc. A third case of acute traumatic sprain evidenced no effect from curare. The sprain was superimposed upon osteoarthritis of the lumbar spine in a gouty patient who had also been suffering for some time from a rather severe anxiety state.

In five patients with acute low back pain *without* sciatic radiation, related to osteoarthritis of the lumbar spine, four obtained prompt, marked relief after the first injection of curare, with practically complete abeyance of distress and marked subsidence of muscle spasm. In the fifth patient, no beneficial effect was observed. The degree of osteoarthritis and the duration of symptoms in the latter case did not differ significantly from that in the other four. Perhaps the fact that this patient was attempting to secure workman's compensation contributed to difficulty in evaluating the effect of curare.

Of the four patients with advanced osteoarthritis of the lumbar spine *with* sciatic radiation of pain, only one definitely benefited from curare. In this case, the sciatica was of reflex origin, unrelated to direct nerve root irritation or pressure. In two patients in whom no improvement occurred, there was evidence of direct sciatic nerve root irritation or pressure. It is significant that in these two cases, back pain and lumbar muscle spasm may have been somewhat ameliorated with curare, but the sciatica was aggravated. In the fourth case the effect of curare was questionable.

In a patient with postural low back strain with lumbar muscle spasm the effect of curare was also only questionable.

Osteoarthritis with Associated Periarticular (Capsular) Fibrositis. Six patients with clinical and roentgenographic evidence of osteoarthritis of peripheral joints with associated periarticular (capsular) fibrositis of either degenerative or perhaps infectious origin were treated.

In two of these patients questionable subjective improvement resulted from the administration of curare. Both were elderly. In both the onset of the fibrositic symptoms followed an acute respiratory infection; the sedimentation rates were accelerated. The findings indicated a capsulitis of apparently infectious origin, superimposed upon marked generalized osteoarthritis. Although these patients reported some alleviation of morning stiffness, the effect was negligible and probably attributable to the general therapeutic measures; rest, analgesics, and physiotherapy used concomitantly with curare.

Four of these patients presented osteoarthritis of the peripheral joints with symptoms indicative of an associated capsulitis of degenerative origin. They all had normal sedimentation rates. In none of these was there evidence of improvement, either objective or subjective, after repeated administration of curare in oil and wax.

Fibromyositis. Four patients with fibromyositis failed to derive any benefit from repeated administration of curare. One of these patients suffered from a generalized fibromyositis following an acute upper respiratory infection. The second patient manifested characteristic fibromyositic symptoms involving the shoulders, hips, and lower back. The fibromyositis in the third and fourth patients was localized to the cervical region.

Psychogenic Rheumatism. Seven patients presented the typical syndrome of psychogenic rheumatism in which a feeling of stiffness, muscle aching, and other types of pain, often bizarre, were associated with other psychoneurotic personality traits. A diagnosis of psychogenic rheumatism had previously been established both by direct examination as well as by exclusion of organic musculoskeletal disease. There was no hope of obtaining any therapeutic benefit in this group; they served as a control. In none of these cases was any improvement noted. Two patients described some degree of subjective improvement, but this, however, did not correspond to the usual description of the effect of curare. Subsequent injections of curare were said to have been of no benefit or to have been followed by actual increased severity of symptoms.

Discussion of Results

The beneficial effects of curare are always evidenced by prompt, dramatic relief of muscle spasm, generally after the first injection of the drug. Hence, long periods of trial are unnecessary. The specific physiologic effect of the drug is so clear cut that when beneficial therapeutic results are forthcoming, they should be evident to some degree after the very first injection. Except in the case of patients with psychogenic rheumatism, the response is generally

repetitive, equally effectively elicited by subsequent injections. The patient with psychogenic rheumatism may describe subjective benefit after the initial injection of curare; but he is susceptible to the influence of suggestion by "an injection" of any type. He may report "much relief" or "improvement" following the initial injection of curare. More detailed questioning with regard to the effect will elicit a quite atypical description. Moreover, subsequent injections of curare in such cases are likely to produce "little" or "no beneficial" effect, or even "more muscle stiffness." Such experiences serve as striking controls for those cases of organic rheumatic states with evidence of muscle spasm, in whom the description of subjective relief generally follows a distinctive pattern. In such cases subjective improvement can be correlated with and confirmed by physical examination which indicates resolution of muscle spasm.

As can be noted in table 1, our results in treatment of muscle spasm in the group of patients with rheumatoid arthritis has been entirely discouraging. Occasionally, subjective relief of muscle spasm was reported, as for example in one case with relief of adductor spasm associated with rheumatoid arthritis of the hips. We were not surprised at the ineffectiveness of curare in the alleviation of muscle spasm in rheumatoid arthritis, especially cases of advanced degree, such as we have treated thus far. It must be remembered that the muscle spasm of rheumatoid arthritis is probably caused not only reflexly by the local joint inflammation, but probably also by infiltration of the muscle mass with an inflammatory exudate, as has been demonstrated by Freund and his associates,[6] and as we have found in many muscle biopsies in rheumatoid arthritis. In rheumatoid arthritis there is, moreover, an inflammatory capsulitis with a certain degree of spasm or contracture of the joint capsule.

We have not had the opportunity of administering curare to patients in the earliest phases of rheumatoid arthritis. It is possible that the drug might prove to be of value in such early cases, before muscle spasm has been seriously complicated by the element of muscular and capsular contracture, and the effect of the inflammatory exudate in the muscle itself. Schlesinger and Ragan,[4] whose experience with curare in rheumatoid arthritis was more favorable than ours, employed the drug in the *acute* phase of the disease: one of the two cases cited by them having had an acute onset of rheumatoid arthritis two months before admission; the other six months before. It would appear from these and our less encouraging results in more advanced cases, that the effectiveness of curare in rheumatoid arthritis will, if at all evident, probably be limited to the earliest phases of the disease.

In the treatment of periarthritis of the shoulder the effectiveness of curare is especially striking. It is most obvious when adhesive changes do not exist and the limitation of movement and pain is caused entirely by muscle spasm. Obviously, curare will not resolve adhesions within the subacromial bursa or between the capsule of the shoulder. But even in adhesive bursitis or capsulitis of the shoulder, curare may be valuable if em-

ployed in conjunction with physiotherapy and manipulative exercises. By overcoming muscle spasm, it may be possible in some of these instances to restore the full range of motion in the shoulder by physiotherapeutic measures, including exercise, when manipulative therapy under anesthesia might otherwise be required. The use of curare is also strikingly beneficial in conjunction with physiotherapeutic measures which we institute promptly after the breaking up of adhesions under anesthesia. In such cases we have found that the therapeutic exercises following manipulation were carried out more easily, with less discomfort, and with a better ultimate result, attained in a much shorter period of time. The number of cases so treated is small, however, so that final evaluation is not possible at this time.

The beneficial results of curare in the relief of low back pain demonstrates the specific value of this drug in the abolition of reflex muscle spasm. Curare should find its greatest field of usefulness in the treatment of low back pain when there is muscle spasm of reflex origin. Our two patients with low back pain (without sciatic radiation) who were not benefited from curare presented associated factors, especially an unfavorable psychogenic component which militated against a favorable result. Their evidence should therefore not detract from the otherwise consistently favorable results in this group of cases.

We found curare to be of no value in low back pain with sciatic radiation caused by nerve root irritation or pressure. These results confirm the observations of Schlesinger and Ragan [4] who also noted that with removal of the splinting action of muscle spasm, sciatic pain resulting from direct nerve root involvement was increased.

Relief of muscle spasm and pain which the use of curare affords in the treatment of periarthritis of the shoulder and low back pain is dramatic. It would be unsound, of course, to discard other proved therapeutic measures specifically applicable to the underlying pathologic lesion. The contribution of curare is the abolishment of the cycle of muscle spasm and pain which often constitutes a most trying and protracted problem. Earlier rehabilitation of the patient is then possible.

In the treatment of osteoarthritis of peripheral joints with associated degenerative periarticular (capsular) fibrositis, curare is generally unsatisfactory. Since the restriction of mobility and pain in these cases is related largely to changes in the joint cartilage and articular capsule and not primarily to reflex muscle spasm, the absence of a favorable response to therapy with curare is not surprising.

Curare has also proved totally ineffective in the syndrome of fibromyositis.

The lack of benefit to be derived from the use of curare in cases of psychogenic rheumatism merely serves to define more sharply the specific problems in which it may be helpful.

Reactions followed the administration of curare in 12 of the 58 patients. For the most part reactions were mild and not disabling, and consisted of

blurring of vision, vertigo, and weakness. Blurring of vision was the earliest manifestation; vertigo, generalized weakness and numbness developed if the reaction was more severe. In two cases the muscular weakness was severe enough to incapacitate the patient completely for several hours. Because of the possibility of such a reaction, curare should not be given to ambulatory patients unless they can reach their homes very shortly after an injection.

Prostigmine methylsulfate intramuscularly or intravenously or prostigmine bromide by mouth may be given to overcome the more severe reactions.

An important precaution is the use of a perfectly dry syringe and needle to prevent formation of water soluble and rapidly absorbed curare which may be responsible for unusually severe reactions.

Summary and Conclusions

1. This report deals with our clinical observations with a slowly acting suspension of d-tubocurarine in wax and peanut oil in the treatment of 58 cases of various types of rheumatic disease, including rheumatoid arthritis. The results justify rather definitive conclusions with regard to the therapeutic effectiveness of curare in the alleviation of reflex muscle spasm only in certain specific rheumatic disorders and its ineffectiveness in certain other types of rheumatic disease.

2. D-tubocurarine in oil and wax has served to relieve the muscle spasm, and indirectly the limitation of motion and pain, in non-adhesive periarthritis of the shoulder. It has facilitated the physiotherapeutic management and recovery and shortened the period of treatment in adhesive periarthritis of the shoulder when manipulation under anesthesia was necessary for breaking up of adhesions.

3. Curare was found to be especially useful in the treatment of low back conditions associated with muscle spasm. Curare affords the most striking relief of symptoms by abolishing muscle spasm in hypertrophic arthritis of the spine and in acute low back sprain, permitting earliest rehabilitation of the patient.

4. Curare was of no benefit in patients with low back syndrome with sciatic pain resulting from direct nerve root irritation or pressure.

5. D-tubocurarine in oil and wax has been practically without effect in the alleviation of the muscle spasm associated with advanced rheumatoid arthritis.

6. In our experience curare has not been effective in relieving the muscle spasm and "stiffness" which occurs in osteoarthritis of peripheral joints with associated periarticular fibrositis. It was totally ineffective in relieving the "stiffness" of primary fibromyositis.

7. As might be expected, curare was also totally ineffective for relief of "muscle stiffness" of psychogenic rheumatism.

8. Reactions from the drug sometimes occur. They are generally mild, but may in some instances cause diplopia, vertigo, and severe muscle weak-

ness. Prostigmine, an antagonist to curare, may be employed to overcome the more severe reactions.

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AN EVALUATION OF RADICAL SURGERY FOR CARCINOMA OF THE PANCREAS AND AMPULLARY REGION *

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The justification for present day radical surgery should be determined by the threat of the untreated lesion, the operative risk if radically treated, the life expectancy after operation, and the prospect of comfortable living subsequently. Radical surgery may be curative, but much of it may be only palliative. This of course is true of many forms of medical therapy.

Radical surgery of the past 15 years, and especially that of today, has been made possible by many factors: a better understanding of supportive treatment, blood transfusion, maintenance of fluid, protein and electrolyte balance, improved methods of anesthesia, intelligent use of chemotherapeutic agents. But above all, a newer generation of physiologically minded and trained surgeons, especially the resident trained surgeons, more interested in an understanding of the needs of the sick, debilitated patient and in restoring his physiological balance, than in the speed of the operation or in showmanship.

The very few earlier attempts, in the first two decades of the century, to resect ampullary growths and the head of the pancreas with a portion of the duodenum proved so hazardous that they were abandoned.[1] In the early thirties, successful removal of islet cell tumors had demonstrated that the pancreas was not an untouchable organ.[2] In 1934, when the attempts to remove carcinomatous growths from the ampullary area were renewed at the surgical clinic of the Columbia-Presbyterian Medical Center,[3] the risk of persistent bleeding in the deeply jaundiced patient required a two stage procedure. But it was demonstrated that the head of the pancreas, with all of the duodenum, the antrum of the stomach, the lower end of the common duct, and the retroduodenal gland-bearing area could be resected.

By 1940, vitamin K therapy had been introduced and by its use the bleeding tendency could be controlled. In March of that year, we[4] carried out the first one stage resection of the above structures in a woman with a carcinoma of islet tissue in the head of the pancreas. This patient is still alive and active.

Since then, many modifications of the one and two stage radical procedures have been successfully carried out, some 220 of them in five of the clinics of this country (table 1). Reports of these procedures are now beginning to come from foreign clinics. Furthermore, since Priestley's[5] first total pancreatectomy for hyperinsulinism in 1944 (this patient is alive and

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well, requiring only 20 to 30 units of insulin per day) some 20 others have been reported.

In these radical procedures, the operative risk, the long term followup, and the comfortable physiology and relief from pain and jaundice depend upon several factors: (1) the type of the carcinoma, (2) the site of the tumor, (3) the early diagnosis of the lesion, before it has spread to the lymph nodes and peritoneum, (4) the radical, en bloc, removal of the growth with part or all of the pancreas, the entire duodenum, the lower end of the common duct, the antrum of the stomach, and the retroduodenal and pancreatic lymph nodes.

The Type of Carcinoma

Carcinoma of the papilla of Vater and the ampullary area is usually a fungating adenocarcinoma, growing into the lumen of the duodenum with a slower invasion of the lymphatics. Carcinomas of the pancreas are more often of the invasive, infiltrating, undifferentiated type, spreading rapidly into the lymph nodes and metastasizing to the liver and peritoneum.

The Site of the Tumor

Ampullary growths obstruct the bile and pancreatic ducts more quickly and completely than those in the pancreas, and give the important warning signal of jaundice earlier. Courvoisier's syndrome of painless jaundice with an enlarged gall bladder is most frequently seen in the patients with ampullary tumors. However, not all of these patients are pain-free, yet the pain is not as severe, constant, or radiating to the back as it is in pancreatic carcinomas of the body or tail.

In carcinoma of the pancreas, the warning signal of jaundice depends upon the proximity of the growth to the common duct. It is usually absent in carcinoma of the body and tail. Pain, as mentioned, is usually more severe and constant, worse on lying down and frequently of a boring character, radiating into the back. The more distant from the ampulla, the later the diagnosis as a rule, and the worse the prognosis.

Early Diagnosis

Aside from the essential history and physical examination, which in many patients establishes the early diagnosis, certain laboratory procedures are helpful and must be emphasized. The most important is the study of the duodenal contents. This is based upon the early sound observations of Pavlov,[6] who demonstrated the effect of increased pancreatic external secretion by vagal stimulation, and of Bayliss and Starling,[7] who demonstrated the hormonal action of secretin in accelerating the flow of pancreatic juice. Since then, Lagerlöf [8] in Stockholm, Comfort [9] and his associates at the Mayo Clinic, and Bauman [10] at the Columbia-Presbyterian Clinic in this country have demonstrated the value of duodenal intubation in the differen-

tial diagnosis of jaundice and of ampullary and pancreatic lesions. In aspirating the fasting duodenal contents by the double tube Lagerlöf technic, the important findings are the amount of bile and presence or absence in it of cholesterol crystals and bile pigment particles, the amount or absence of pancreatic juice, the presence of red blood cells, the presence of tumor cells.

Marked diminution or absence of bile and pancreatic juice, with the presence of red blood cells or tumor cells, indicates a carcinoma of the papilla. Normal amount of pancreatic juice with marked diminution or absence of bile plus red blood cells points to a carcinoma of the common duct. Normal bile but diminished or absent pancreatic juice plus red blood cells implies a carcinoma of the pancreas. Cholesterol crystals or bile pigment particles indicate the presence of gall stones. The finding of tumor cells in the centrifuged specimens establishes the diagnosis of neoplastic disease. Ampullary carcinoma was diagnosed last November at the Memorial Hospital by the finding of tumor cells, and proved by a radical pancreatoduodenectomy. Jaundice with an elevated serum phosphatase means obstruction of the common duct. Absence of jaundice does not rule out a growth in the pancreas.

Careful barium roentgen-ray studies of the duodenum may show a filling defect by a fungating growth of the ampulla or a distortion or increase in the C-curve of the duodenum, the result of a tumor in the head of the pancreas.

The only hope of permanent results with radical surgery in these cancers is the early diagnosis of localized lesions. In the majority of cases, the general practitioner and the internist are first consulted, and are responsible for prompt and early diagnosis, or a fatal delay by studying the patient until the diagnosis is obvious and the lesion inoperable. The internist is as important as the surgeon in the cure of these patients.

Results

The average life expectancy in carcinoma of the pancreas treated expectantly is about six months. A palliative bile shunting operation, preferably a cholecystojejunostomy, relieves the patient of intolerable pruritus and temporarily improves digestion, and should be done if the growth is found inoperable.

During the first 10 years of this radical surgery, the operative mortality was high in the 30 per cent level. But with the improvements in pre- and postoperative therapy and in the operative technic, this hazard has been markedly reduced. Cattell [11] has the remarkable record of a 13.6 per cent mortality in 59 patients. He has carried out pancreatoduodenectomy in 22 patients with ampullary growths, with only one death.

Drs. Parsons and Lockwood [12] have not lost a patient in their last 13 radical procedures. Dr. Waugh [13] of the Mayo Clinic has lost only one patient in the last 15 pancreatoduodenectomies.

The radical surgery for ampullary carcinoma gives better results than for carcinoma of the pancreas itself. From the five clinics mentioned, eight

patients lived five years or more, after removal of ampullary growths—two of them over seven years. Of the collected cases of carcinoma of the pancreas, three have survived five years or more,—two of them operated upon by Brunschwig.[14] One of these, the first one stage radical resection for carcinoma of islet cells, is living over nine years, but may have liver metastases at present. This is not a functioning islet cell tumor, however. In Cattell's [11] largest series of 59 patients operated upon for carcinoma, 30 per cent lived three years or more.

The fact that it has been demonstrated that cancer cells can be readily found in pancreatic duct fluid in cases of pancreatic carcinoma, and that trypsin favors the transplantation of cancer cells in experimental animals [15] would explain the high incidence of recurrence in resection of the pancreas, and may be a definite indication for a total pancreatectomy in patients with carcinoma of the pancreas.

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THE USE OF MIXTURES OF PROTAMINE ZINC AND REGULAR INSULIN *

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DURING the past 10 years a considerable experience in the use of adjustable mixtures of protamine zinc and regular insulin in the Section on Metabolism Therapy of the Mayo Clinic has led to the formation of certain opinions about the usefulness and limitations of this method of insulin therapy of diabetes. Among other things, it has become apparent that appropriate mixtures, because of the intermediate character of their action with respect to onset, intensity and duration, have great usefulness in cases of moderately severe to severe diabetes. It is in these cases that protamine zinc insulin, used alone, lacks sufficient intensity of action to prevent undesirable degrees of postprandial hyperglycemia and glycosuria while still retaining a capacity for causing serious hypoglycemia during the fasting hours of the night.

It is my purpose in this paper to describe the background for our present opinions about the use of mixtures of protamine zinc and regular insulin, and by way of illustrating the place of mixtures in the therapeutic scheme, to analyze the types of insulin therapy employed in 246 patients with diabetes seen late in 1948 and early in 1949.

This group of patients, as well as the diabetic practice of the clinic in general, requires description, for the character of the practice has some bearing on the interpretation of results. Approximately half of all the diabetic patients seen in the clinic each year are treated as ambulatory patients. Most of these take their meals, according to individually prescribed diet formulas, in the Rochester Diet Kitchen.† All of the patients to be described herewith were ambulatory outpatients throughout the period of their treatment and instruction. Hospital patients were excluded from consideration because of the common presence in them of complicating medical or surgical conditions which make the results of therapy of diabetes more difficult to evaluate. The group to be described probably included more than the usual proportion of "difficult" conditions, from the standpoint of diabetic management, because many of these patients were referred to the clinic for advice when major problems in their management were encountered at home. The

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† The diet kitchen provides a means whereby fairly rigid dietary control of diabetes can be maintained while the patients are ambulant and receiving instruction in the management of their disease. All servings of food are weighed or carefully estimated according to the requirements of the individual patient. Experience has shown that the patients learn more quickly and more satisfactorily when ambulant outpatients than they do in the hospital. From day to day they are permitted to assume increasing responsibility in their own care.[1] By exchanging notes and experiences with other ambulant patients, and having regular conferences with physician and dietitian, the learning process is accelerated.

period of observation of these patients was often shorter than desirable, so that in many instances the daily dose of insulin was considerably more at the time of dismissal than it subsequently became at home, and the control of glycosuria in some instances was not the best attainable.

The fact that the response of diabetic patients to treatment differs is frequently overlooked. That such variability actually exists is illustrated by the well-known fact that in almost half of all cases of diabetes the disease is well controlled by diet therapy alone, while in the other half insulin in addition to diet is necessary. Furthermore, among patients who require insulin there is a great variability in response to treatment. The reasons for this variability are not well understood. It may perhaps indicate that there are different forms of the disease, different etiologic factors, or possibly only differences in the intensity of the disease. In any event, it is important to be aware of the inherent ease or difficulty of therapy in different diabetic patients before a program of administration of insulin is chosen in any given case, and before the merits of any particular system of therapy employed in a group of cases are judged.

Stated simply, in some diabetic patients the disease is easily controlled by almost any program of administration of insulin, whereas in others the timing characteristic of the action of the insulin employed must be carefully tailored to the needs of the individual. In the latter group of cases a relatively intense insulin action usually is needed during the day when food is being ingested, and a relatively feeble insulin action, during the fasting hours of the night. Insulin therapy to be effective in cases of severe diabetes must be arranged so that account is taken of the fact that the human subject eats during the day and fasts during the night. Furthermore, there is a small group of patients—those who have so-called unstable or brittle diabetes—in whom it is virtually impossible to maintain sugar-free urine and freedom from insulin reactions with any type or combination of insulins now available. In this group it seems that nothing short of an "automatic" insulin, with rate of absorption determined by the level of the blood sugar, would accomplish precise control. Unfortunately, there is at present no indication that an insulin with such a high order of intellect will ever be developed.

Development of the Use of Mixtures of Insulin

In this country Colwell,[2] MacBryde,[3] Peck [4] and others have made intensive studies of the action of mixtures of regular and protamine zinc insulin in diabetic patients. Colwell,[2] in particular, in a series of excellent papers published since 1942, has described with considerable precision the timing characteristics of mixtures of varying proportions of regular and protamine zinc insulin. Briefly, it has been shown that it is necessary to mix at least one part of regular with one part of protamine zinc insulin to secure definite modification of the action of the latter. Intensification and shortening of action is not sufficiently marked to be therapeutically useful

until a ratio of 2 units of regular to 1 unit of protamine zinc is reached. With additional increases in the proportion of regular insulin, the action of the mixture is further intensified and shortened. The obvious implication is that appropriate mixtures should be superior to protamine zinc insulin from the standpoint of control of postprandial glycosuria during the day and prevention of hypoglycemic reactions at night in the patient with severe diabetes.

In contrast to the experimental studies of Colwell, our own acquaintance with the action of mixtures has been based almost exclusively on their clinical use. Shortly after Lawrence,[5] in 1938, published a brief description of the treatment of diabetes with mixtures, we in the Section on Metabolism Therapy at the Mayo Clinic began to treat certain types of diabetic patients with mixtures and have been doing so ever since.

The development of our knowledge of the action of mixtures, on the basis of clinical observation, makes an interesting story. Initially, in 1938, we started to combine in one syringe the doses of regular and protamine zinc insulin which we had previously been giving in separate sites. Consequently the early mixtures consisted of relatively small amounts of regular insulin and relatively large amounts of protamine zinc insulin. Thus, it was not uncommon for the patient with severe diabetes to receive a mixture consisting of, say, 40 units of protamine zinc and 10 units of regular insulin. With close observation of numerous patients, it became apparent before long that the action of such mixtures closely resembled that of protamine zinc insulin alone. In patients with severe diabetes, insulin reactions tended to occur between midnight and the time for rising, and excessive glycosuria during the day was almost the rule. In other words, the use of such mixtures offered no particular advantage, for the difficulties for which regular insulin was added to protamine zinc insulin remained uncorrected.

Eventually we added more regular insulin to the mixtures, in an effort to reduce glycosuria during the day and decreased the amount and proportion of protamine zinc insulin in an effort to prevent the insulin reactions which our patients were experiencing too frequently in the early morning hours. Before long we were finding that the great majority of patients with diabetes of sufficient severity to require the use of mixtures were being treated with mixtures containing as much, or more, regular insulin as protamine zinc insulin. By 1940 or 1941 it had become apparent that in most cases in which mixtures were employed, the ratio of regular to protamine zinc insulin lay between 2 : 1 and 3 : 1.

At the same time it became obvious, as had been anticipated, that the mixtures which contained higher proportions of regular insulin actually did provide better control of daytime glycosuria and did lessen the hazard of nocturnal insulin reactions in patients with severe diabetes who had formerly been treated with protamine zinc insulin alone. Thus, by a fairly prolonged process of clinical trial and error, we arrived at an appreciation of the timing of the action of mixtures which coincided in all essential respects with Col-

well's descriptions of their action, arrived at by rigidly conducted experimentation.

One further digression is necessary before proceeding to a consideration of the treatment employed in our recent group of cases. This concerns the vexing questions of what constitutes control of diabetes and, once control has been defined, how important is it? Is it necessary to set one's therapeutic goal any higher than the simple avoidance of ketosis and severe insulin reactions? These questions have not yet been answered satisfactorily, and he who pretends to know the answer is basing his opinion more on feeling than on actual knowledge. I am personally of the opinion that control (or lack of it) is probably not the only, or even the crucial factor in the prevention (or development) of the so-called degenerative complications of diabetes, arteriosclerosis, retinopathy, neuropathy and intercapillary glomerulosclerosis, which are being observed with increasing frequency among diabetic patients who have been kept alive for many years by use of insulin. Nevertheless, as Ricketts [6] has pointed out, the burden of proof is on the one who says that control is unimportant. Prolonged periods of unbridled glycosuria, perhaps associated at times with mild ketosis, might well be one factor in the development of degenerative complications, even if not the sole factor. Therefore, until the contrary is proved, we should continue to strive for as precise control of glycosuria as is possible and compatible with a reasonably simple program of treatment and the avoidance of insulin reactions.

Types of Insulin Therapy Recently Employed

Now to proceed to a consideration of the types of therapy employed in the recent group of 246 ambulatory diabetic patients. This particular number of patients was chosen for study because it included exactly 100 patients who were treated with extemporaneous mixtures of regular and protamine zinc insulin. These 100 patients will be subjected to closer scrutiny than the rest because it is treatment with such mixtures that interests us at this time.

First, it will be noted that of the total of 246 patients, 96 (or 39 per cent) required only diet therapy, without the use of insulin, for control of glycosuria (table 1). We have made a practice of omitting insulin only in those cases in which the urine is demonstrated to remain consistently free of sugar while the patient is on an adequate diet without the use of insulin. This figure is somewhat lower than that for the total diabetic practice of the clinic,

Table 1

Therapy Employed Recently in 246 Cases of Diabetes Mellitus (1948–1949)

Therapy	Cases	Per cent
No insulin	96	39
Insulin	150	61

probably because a large number of patients with mild diabetes are excluded who were not treated as ambulant patients or who were seen in the hospitals for reasons unrelated to the presence of diabetes. Among the 150 patients who were treated with insulin two of every three were taking mixtures at the time of their dismissal from our care (table 2).

TABLE II

Insulin Therapy Employed Recently in 150 Cases of Diabetes Mellitus (1948–1949)

Insulin	Cases	Per cent
Protamine zinc	36	24
Regular only	0	0
Mixed regular and protamine zinc	84	56
Mixed regular and protamine zinc plus supplementary doses of regular	16	11
NPH 50	5	3
Globin only	9	6
Total	150	100

The percentage of patients who were treated with a single dose of protamine zinc insulin taken in the morning before breakfast is relatively small (36 cases or 24 per cent of those for whom insulin was used), probably much smaller than in many other large diabetic clinics (table 2). Furthermore, it is noteworthy that in only two cases out of the 36 was a daily dose of protamine zinc insulin in excess of 20 units employed (table 3). This is an indication of our great respect for the hazard of nocturnal hypoglycemic reactions from large doses of protamine zinc insulin, and our belief that most patients who have diabetes of sufficient severity to require more than 20 units of insulin daily maintain better control of glycosuria when they use an insulin having the timing characteristics of appropriate mixtures rather than of protamine zinc insulin alone. In other words, a daily requirement for insulin in excess of 20 units has become in our practice an indication for the

TABLE III

Doses of Protamine Zinc Insulin

Daily dose	Cases	Per cent
20 units or less	34	94
More than 20 units	2	6
Total	36	100

use of an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin. Obviously, there are a few patients who might be excepted from this policy if experience has shown that they maintain good control of glycosuria and freedom from insulin reactions while taking larger doses of protamine zinc insulin. Nevertheless, in our

experience, these same patients get along equally well with mixtures, and we believe more safely. Indeed, it seems that all patients now treated with protamine zinc insulin would fare equally well with an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin.

It has already been pointed out that in the early days of the use of mixtures it was found by a rather tedious process of clinical trial and error that the best control of severe diabetes and the greatest freedom from insulin reactions were attained with mixtures containing 2 or 3 units of regular insulin for every 1 unit of protamine zinc insulin. The experience of recent years has continued to verify this early impression. The strong effect of such mixtures tends to prevent excessive glycosuria during the day, while the prolonged effect prevents escape from control overnight. There is sufficient

TABLE IV

Mixtures of Regular and Protamine Zinc Insulin in 100 Cases of Diabetes Mellitus

Ratio of regular to protamine zinc insulin	Cases
Less than 1:1	2
1:1 to 1.5–:1	4
1.5:1 to 2–:1	19
2:1 to 2.5–:1	54
2.5:1 to 3–:1	13
3:1 and higher	11

overlapping of the effects of doses on successive days to provide additional insurance against serious loss of control due to the waning of action of one dose before the next one begins to act. The more severe the diabetes, or the higher the carbohydrate content of the diet, the more likely is the ratio to be in the neighborhood of 3:1 rather than 2:1. It will be noted that for 67 of the recent series of 100 patients treated with mixtures, the ratio of regular to protamine zinc insulin was between 2:1 and 3:1 (table 4). With longer periods of observation of the patients the proportion of mixtures in this range would probably be increased, for many of the patients who had mild diabetes and used low ratios at the time of dismissal eventually were stabilized on small doses of protamine zinc insulin alone.

DIFFICULTIES IN THE USE OF MIXTURES

It is perhaps unnecessary to point out that mixtures do not solve all the problems of treatment of patients who have diabetes of the type which has been described as "brittle," "labile" or "unstable." The diabetes of a few of these patients remains difficult to control with mixtures or any other form of insulin therapy. While these patients have the most severe type of diabetes from the standpoint of difficulty of control, they do not necessarily

require large doses of insulin. Labile behavior is sometimes observed in diabetic patients who require only 15 to 20 units of insulin daily. For the most part, however, the daily requirement of patients who have labile diabetes is more than 40 units. It can be said without qualification that protamine zinc insulin, used alone, is not good treatment for this type of diabetes. Attempts to treat brittle diabetes with protamine zinc insulin alone almost inevitably lead to two kinds of trouble, namely, poor control of glycosuria during the day when food is being ingested, and hypoglycemia during the night.

Fortunately, some of these patients get over their labile behavior with continued careful treatment, and behave well on conventional management with a combined dose of protamine zinc and regular insulin once daily. Some of those who do not get over it are able to maintain reasonably good control by taking the mixture of protamine zinc and regular insulin in divided doses before the morning and evening meals, about two thirds in the morning and one third in the evening. One dose of globin insulin usually is a failure in these cases, but two doses, one before breakfast and the other before supper, may be as satisfactory as a divided dose of a mixture of protamine zinc and regular insulin. Multiple (three or four) doses of regular insulin seem to be the best expedient in an occasional case, in spite of the inconvenience of such a program of treatment.

The objection is frequently raised that the use of mixtures of protamine zinc and regular insulin is too complicated a procedure for the majority of diabetic patients. We feel that we have been able to overcome this objection in most instances by careful and sometimes prolonged instruction. The majority of patients, in our practice, including those of seemingly mediocre intelligence, are able to master the technic of preparing and injecting the mixtures and adjusting the doses of the two components. In the occasional case in which difficulty is experienced some alternative method of treatment is used which is simpler from the standpoint of the patient, such as globin insulin or multiple doses of regular insulin.

Even though it has been our experience that the majority of patients are able to master the difficulties involved in the use of mixtures in the same syringe, it cannot be denied that this method of treatment is somewhat inconvenient. An escape from this inconvenience in many cases of diabetes would be provided by the availability of a fixed modification of protamine zinc insulin which has an action like that of a 2:1 mixture of regular and protamine zinc insulin. Such a fixed modification is insulin type NPH 50, recently available for trial. This was used in only five cases of the group which has been described. However, before and since this group of cases was seen, experience with NPH 50 has been more extensive and has been reported by Kirkpatrick.[7] We have become convinced that such an insulin, if generally available on the market, would obviate the need for modification of protamine zinc insulin by the patient in many cases, for it fills the needs of the majority of the patients who are now treated with mixtures. Further-

more, it can be expected to give satisfactory results in all the patients who are now successfully treated with small doses of protamine zinc insulin alone. In the few cases of severe diabetes in which higher ratios of regular to protamine zinc insulin are required, supplementation with additional amounts of regular insulin is easily accomplished in accordance with the needs of the individual patient. Fortunately, the addition of small amounts of regular insulin to insulin type NPH 50, unlike the addition to protamine zinc insulin, results in definite intensification of its action.

The principles involved in the adjustment of the two kinds of insulin comprising a mixture are relatively simple. In the first place, as has already been mentioned, it was learned by experience some time ago that the majority of patients who are treated with mixtures of insulin obtain the best control when the amount of regular insulin is two to three times the amount of protamine zinc insulin. In the actual regulation of diabetes of a patient, one can proceed as follows: The test for sugar in a fresh specimen of urine voided in the morning before breakfast is used as a criterion of the adequacy of the dose of protamine zinc insulin taken 24 hours previously. The dose is so adjusted that there will be no nocturnal reactions, and little or no sugar in this specimen, preferably none. Likewise, the test of a fresh specimen voided late in the afternoon before supper serves as an index of the adequacy of the dose of regular insulin taken that morning. This dose is adjusted so that reactions will not occur during the day, and there will be no more than a trace of sugar in this specimen. Changes in the dose of protamine zinc insulin are usually made in steps of 2 units, since this dose is relatively small, while changes in the dose of regular insulin, which is usually at least twice as large, are usually made in steps of 4 units. The patients are carefully instructed in the method of adjustment, for frequently further adjustments of the dose are necessary at home, particularly if the period of observation under the direct supervision of the physician is short.

Summary

The timing characteristics of appropriate mixtures of protamine zinc and regular insulin are well adapted to the needs in many cases of moderately severe to severe diabetes. Such mixtures provide the requisite intensity of insulin action during the day when food is being ingested, and a prolonged action of low intensity for maintenance of control of diabetes overnight. An effective proportion in most instances is between 2 and 3 units of regular insulin to 1 unit of protamine zinc insulin.

A fixed modification of protamine zinc insulin having an action like that of a 2:1 mixture of regular and protamine zinc insulin such as insulin type NHP 50, could be employed with satisfactory results in many more cases than the standard protamine zinc insulin which is now available. Its action could be further intensified and shortened by the addition of regular insulin when necessary.

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SUMMARY OF EVIDENCE RELATING LIFE SITUATION AND EMOTIONAL RESPONSE TO PEPTIC ULCER *

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THE evidence connecting the occurrence and recurrence of peptic ulcer to emotional conflicts in the life situation has been recently reviewed by Wener and Hoff.[1] The relationship has not as yet been definitely established, but on the basis of studies from several points of view and with a variety of technics, it seems highly likely that some peptic ulcers, at least, occur as part of a biologic pattern which is set in motion in reaction to stresses and strains involving chiefly problems of interpersonal relationship. The data in support of this view are outlined briefly below.

First, it has been known for many years that the stomach of the subject with duodenal ulcer is a hyperfunctioning one, that is, it is red, secretes relatively large amounts of acid, is relatively hypermotile and empties in a comparatively short time. When it has been possible to induce experimental peptic ulcer in animals, the condition has been preceded and accompanied by intense engorgement of the gastric mucosa.[2, 3, 4]

In our studies on the fistulous subject, Tom, we found by direct observation of the gastric mucosa and simultaneous collections of gastric juice and recording of motility that this hyperfunctioning state could be induced by situations which engendered anxiety associated with feelings of hostility and resentment.[5] We found, moreover, that the stomach under these circumstances was hyperemic, turgid and engorged. When, under circumstances of sustained resentment, this pattern of gastric hyperfunction was prolonged, the pain threshold of the stomach was significantly reduced. This led to localized epigastric pain following the application of stimuli such as pinching or Faradic current, which were ordinarily non-noxious. Likewise, gastric contractions of a force and magnitude which would ordinarily not arouse sensations became painful. Thus, in the absence of ulceration but in the presence of sustained gastric hyperemia and hyperfunction, the characteristic ulcer symptoms of epigastric pain relieved by food or alkalis were frequently observed.

Not only was lowering of the pain threshold observed to accompany gastric hyperfunction in association with sustained conflict, but a second physiologic hazard was also observed under these circumstances, namely, increased fragility of the mucous membrane. When the stomach was in an

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average state of activity and the membrane relatively pale and flat, it was possible to strike it sharply with a blunt glass rod or draw a dry gauze square over it without producing any visible lesion. In association with sustained hyperemia, however, such minor traumata resulted predictably in small erosions and bleeding points. Indeed, not uncommonly, such erosions and bleeding points appeared spontaneously in association with a period of unusually vigorous contractile activity. One such spontaneously occurring erosion was kept in contact with gastric juice with a titratable total acid of 90 for half an hour. Mucus accumulated rapidly in the region, but it was removed at frequent intervals by suction through a small glass tube. The acid gastric juice was then reapplied to the bare mucosa. A sharp acceleration of acid and concomitant hyperemia of the whole stomach mucosa occurred and persisted for half an hour after the submersion of the hemorrhagic lesions was discontinued.

Comment. In this phenomenon may lie an explanation of the persistent hyperacidity regularly encountered in persons suffering from gastritis and peptic ulcer. The fact that the base of the ulcerated lesion which is constantly bathed in acid gastric juice effects a further stimulation of acid secretion indicates that afferent impulses subserve this reflex without sensation resulting. It is likely, however, that pain would follow an adequate chemical stimulus.[6]

Experimental Production of Ulcer. The most peripheral edge of the collar of mucosa which lay exposed on the abdominal wall lacked adequate protection owing to defective formation of mucus in this region. A small erosion which occurred on this peripheral edge was exposed continuously to the digestive action of gastric juice for four days. During the first 24 hours, the denuded surface increased in size. It bled intermittently. At the end of four days, it exhibited the typical punched-out appearance of a chronic peptic ulcer, with well-defined edges and a granulating base. It measured approximately 4 mm. in diameter, 1 mm. in depth, and was growing rapidly (figure 1). Traction or pressure on this lesion resulted in pain of a dull, gnawing character, localized in the region of the lesion itself. Throughout the four-day period, the whole mucosa was relatively engorged, and the rate of acid secretion significantly elevated. At the end of four days, because of the hazard to the subject, it was felt that the experiment could not be allowed to continue. The ulcer and surrounding area were covered with a protective petrolatum dressing. Within three days, complete healing had taken place leaving no trace of the lesion behind.

Mechanism of Gastric Hyperfunction. The pathways whereby the impulses reach the stomach which induce potentially harmful gastric hyperfunction associated with situational conflicts are unknown, but have been suspected of lying in the vagus nerves. The clinical evidence derived from the practice of vagotomy for peptic ulcer supports this view, since healing has taken place and a negligible number of ulcers have recurred following sur-

gical procedures considered to have divided all of the parasympathetic innervation to the stomach. Additional confirmation derives from an experiment performed in our laboratory on a second fistulous subject whose fistula was made prior to the attempted surgical removal of a carcinoma of the esophagus.[7] During the latter procedure, it was necessary to section the vagus nerves above the diaphragm. Thus, direct observations were available on the stomach before and after vagotomy. Experimental procedures similar to those performed on Tom were carried out on this subject, his gastric mucosa being viewed through a Brown-Buerger cystoscope. During one of the experimental periods prior to vagotomy the appearance and manner of the subject indicated a sharp change from his usual, quiet friendliness. His face was red, and he appeared exasperated and irritable. He had complained of stiffness and back pain ever since the previous experiment, and confessed that he was angry at having come down to the laboratory again in view of the apparent delay occasioned in his operation.

FIG. 1. Drawing of ulcerated lesion induced experimentally on the gastric mucosa of Tom.

The subject's stomach was examined and found to be much redder and more engorged than before, about 70 on the scale in contrast to the previous 50. He was more voluble and talkative. Asked about his concern regarding his condition, he said that he was reminded of the first doctor whom he had consulted for difficulty in swallowing. The latter had focused his attentions on the stomach, much to the annoyance of the patient. "He was so dumb. I told him it wasn't my stomach, because I knew I couldn't swallow right. He made me waste four weeks fooling around." On this occasion, there occurred much more spontaneous motor activity in the stomach than before. The mucous membrane was so turgid that the minor traumata incident to the instrumentation with the cystoscope caused bleeding. The subject's dominant mood during this interview was anger coupled with hostility and strong feelings of frustration. His stomach displayed the pic-

ture of hyperactivity so characteristically found in the subject, Tom, during situational conflicts productive of aggressive attitudes.

Approximately three weeks following vagotomy, an opportunity was afforded to repeat these observations under similar circumstances. On the third experimental occasion following vagotomy, the membrane was pale, 40, and the folds appeared especially thin. After the baseline observations, an attempt was made, as before, to induce anger and resentment in the subject by discussion of the doctor who had failed to diagnose his condition when he first consulted him. As on the occasion prior to vagotomy, he appeared to become significantly angered, with flushing of the face, loud voice and aggressive gestures, "I think he is crazy. I only went to him because he is around the corner. He said the lining was off my stomach, and gave me some stuff that made me feel lousy—last winter I had some crushed toes. He messed them up, too. He's a God-damned quack, and exile. He charged me enough—$8 a treatment. I'll tell him off." During this outburst, the patient's stomach was continuously under observation through the cystoscope, but, despite the redness of his face, there occurred no detectable change in the appearance of his gastric mucosa (figure 2).

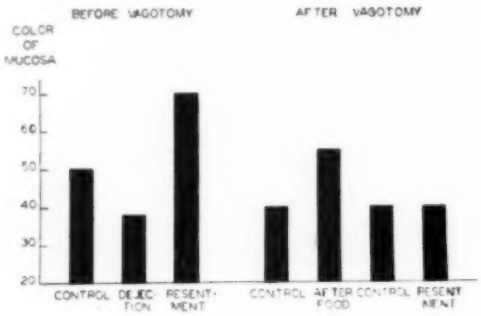

FIG. 2. Changes in the appearance of gastric mucosa under various circumstances before and after vagotomy. Note that vagotomy does not abolish the chemically mediated hyperemia associated with eating.

Comment. A negative result with failure of the stomach following vagotomy to become engorged during anger in this single case does not necessarily implicate the vagus as a route by which impulses reach the stomach which are responsible for gastric hyperfunction occurring in response to situational threats. Further evidence leading to this inference, however, has been adduced by Szasz et al.[8] that an acceleration of acid secretion in subjects with peptic ulcer could be induced by arousing them to anger, but that such an acceleration of acid secretion did not occur following vagotomy.

Clinical Peptic Ulcer. Although the above data establish the fact that

transitory and even sustained alterations in gastric function occur in company with emotional conflicts and that such changes may be associated with epigastric pain, it remains to correlate such reactions to stress with gastric changes and symptoms in subjects with the actual clinical peptic ulcer. The coincidence of onset and exacerbation of the ulcer syndrome in association with difficult life situations is a familiar bedside observation. Mirsky and associates have shown an increase in concentration of a proteolytic enzyme in the blood and urine of subjects with peptic ulcer and especially in situations of significant personal conflict.[9] Experimental correlation of conflict with gastric hyperfunction and symptoms was reported by Mittelmann and Wolff [10] and more recently additional evidence on this point has been collected as detailed below.

Case 1. A 44 year old civil service employee had complained of gnawing epigastric pain on and off for 20 years. His father had been a gentle, retiring person and his mother a matriarchal woman, intensely ambitious for her children. His two older brothers were able to adjust satisfactorily to this setting, the oldest by graduating from medical school, the second one by adopting a rebellious attitude and becoming a professional gambler instead of a lawyer as his mother had wished. The patient felt the need to compensate for his brother's indifference, and took pre-medical work in college. He did poorly, and tried engineering instead. After failing that, he abandoned college. In this setting, he had his first symptoms of epigastric pain, and a duodenal ulcer was demonstrated by radiologic examination. He later obtained a civil service job as a draftsman, and became engaged to a warm, sympathetic girl. Symptoms disappeared during this interval, until the girl died of rheumatic heart disease a few months later. The patient's mother also died at approximately the same time. Within a few months he married an authoritarian, cold and financially ambitious woman. She disapproved of his social relationship with men friends, and eventually forced him to give up lodge activities, from which he derived great satisfaction. Shortly after his marriage, the patient's ulcer symptoms recurred, and they have remained chronic ever since. Several exacerbations and two episodes of hemorrhage have coincided with periods in which his wife seriously disparaged his competence as a man. The following experiment, shown graphically in figure 3, illustrates the relevance of his conflicts concerning his wife to his gastric disturbance.

Ten minutes after the end of a spontaneous period of vigorous gastric motor activity and during a period of almost complete absence of contractions, an interview was undertaken in which the patient was reminded that, in contrast to the high regard in which he had been held by his lodge associates, his wife considered him inadequate as a provider, companion and sexual partner. He became grim and tense, clenched his jaws frequently and said, "it's been a fight all along, and now I got no more fight left in me. I'm caught like a rat in a trap." Promptly, forceful gastric contractions began, and by the end of the interview, a state of incomplete tetanus had been established. Acid secretion was also greatly enhanced, exceeding the level observed during the earlier period of spontaneously increased gastric function. By this time, the subject had begun to groan with pain. Shortly thereafter, during attempts at reassurance and diversion, the evidences of gastric hyperfunction subsided, and with them the symptoms.

Case 2. A 34 year old Italian income tax collector had his first episode of ulcer pain at age 16 in a setting of conflict with his father over retaining a job as auto paint sprayer, which he considered beneath his capabilities. The patient had resented his father from an early age. "My earliest recollection is lying awake at night worrying and thinking about the way my father was making sexual advances toward

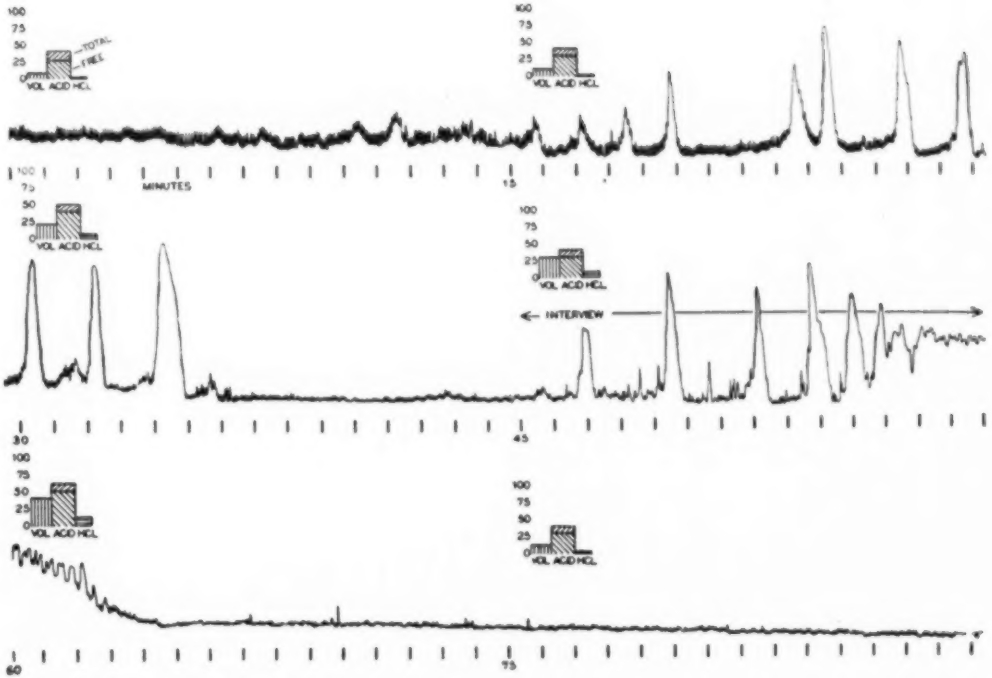

FIG. 3. Changes in motor activity and acid secretion in an individual with peptic ulcer (case 1) during an interview concerning significant personal conflicts.

my mother. I was always relieved if I saw my father go to bed first and my mother stay in the kitchen." The father was a cold, irascible individual who shared the "old country" point of view that a man's sons should work to support him as soon as they could be taken from school. The patient, on the other hand, was eager to go through college and become an engineer. He had grown up in a neighborhood in which there were a good many Jews, and it was a common pattern among the Jewish parents to make unusual sacrifices to provide professional education for their children. Both the patient's father and his younger brother, who also was caught in a conflict between the cultural pattern of his father and his neighborhood, developed peptic ulcers. In addition to his limited educational opportunities, the patient felt that another serious handicap was his small stature. He effected a truculent manner as a child, and got into a great many fights, which he considered "prophylactic," as a means of avoiding being "pushed around" by other people. He could not bear to be laughted at, and was especially sensitive to any slight, real or imagined, to his dignity and competence. He finally obtained a job as an income tax collector, and married an ambitious woman. They had one daughter. He always had difficulty satisfying his wife sexually because of premature ejaculation. She was also dissatisfied with his fixed earnings and lack of progress in the civil service job. The patient noted epigastric pain off and on with exacerbations during periods of stress and conflict and remissions during periods of relative security. "It makes me worse if anyone crosses me. I tighten up and my stomach hurts. When I can relax my stomach improves." He had a gastrointestinal hemorrhage which occasioned admission to the hospital, when a conflict developed between his wife and his favorite sister. During his period of hospitalization he improved markedly with rest, reassurance and without special attention to diet except for frequent feedings. During an asymptomatic period he was intubated with a recording balloon and a Levine tube for collection of the gastric juice. Specimens were withdrawn every 15 minutes. Free and total acid were determined by the usual colorimetric technics. Hydrochloric acid production was calculated with recourse to the methods of Hollander described elsewhere.[5] The acid values and motility pattern are recorded in figure 4. Fifteen minutes after a period of spontaneous motor activity at a time when the gastric musculature is relatively refractory, a discussion was begun of a humiliating experience which he had had on the ward. "An Italian fellow called me a name in Italian. I'm not a dope that I have to take that. He did it again. Later in the day I was lying in bed with a pain and he said 'This is a hell of a time for you to be lying in bed.' I told him it was none of his business, and not to bother me. Now he won't speak to me, and that's what I want. I think I'm entitled to the same respect I give out. Whenever anyone makes a crack at me I have two of them to throw back. I think I'm pretty sharp about solving problems." During the discussion, he was tense, restless and red-faced. Vigorous motor activity occurred and increase in acid output associated with epigastric pain. After approximately 25 minutes, the patient was strongly reassured and the conversation was turned to diverting topics. The gastric motor activity stopped and the pain subsided.

Case 3. A 47 year old Jewish lawyer had had peptic ulcer for 23 years. He was the only child of Russian immigrant parents. The father was a quiet, reflective, religious man, but the mother was intensely ambitious and hard-working. She and the father made severe financial sacrifices to provide the patient with an education. He did well in college and law school, and during the course of these years he changed his name to a more easily pronounced, anglicized form. He also married a Roman Catholic girl. His parents disapproved of this marriage, but condoned it, their principal concern being their son's "success in his career." Shortly after graduation from law school, he was taken into a firm of all gentile lawyers. He soon became heavily relied upon, and was doing much of the difficult work of the office. The partners persistently failed, however, to admit him to the firm. This was the source of great disappointment

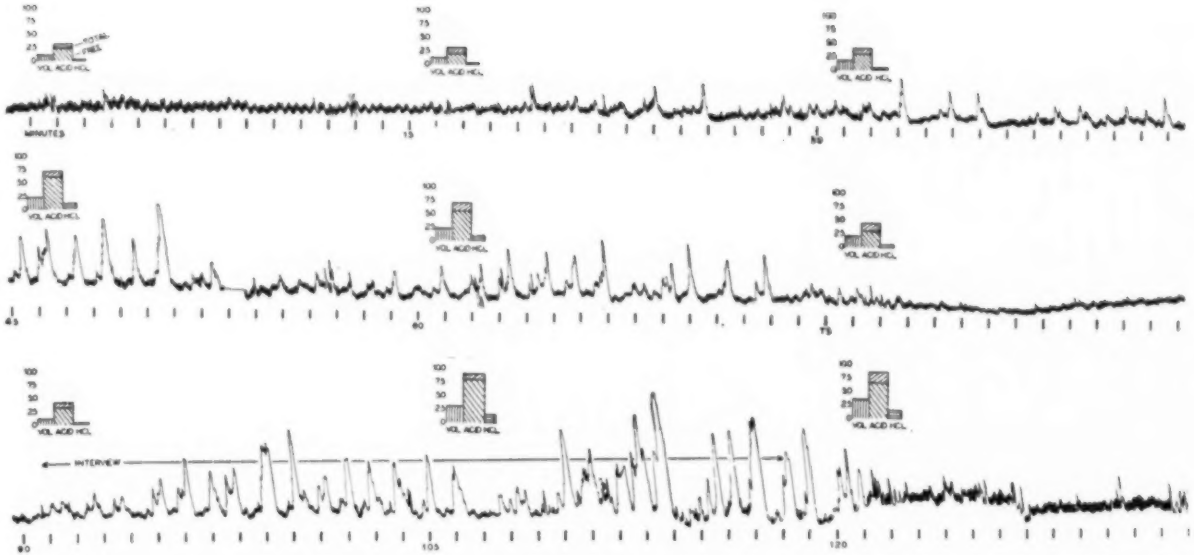

FIG. 4. Changes in motor activity and acid secretion in an individual with peptic ulcer (case 2) during an interview concerning personal conflicts.

and frustration, not only to himself but to his mother and wife, who, like his mother, was intensely ambitious. It was in this setting that ulcer symptoms first developed.

Finally, when it appeared that the partners could no longer exclude him from the firm, they hired a second Jewish lawyer. The head of the firm then told the patient that he felt unjustified to take one of these men and not the other into the firm. This occasion was followed by a severe episode of gastrointestinal bleeding, for which the patient was hospitalized. Finally, at the outbreak of World War II, the younger Jewish lawyer was taken into the Army. The older members of the firm were often preoccupied with matters outside the office, and thus the patient's duties and responsibilities were redoubled. He was virtually running the law office. Despite the heavy work and long hours, his ulcer symptoms disappeared, and throughout the period of the war he felt well. At the conclusion of the war, however, his associate returned from service unharmed, and again the frustrating situation was resumed. The patient's epigastric pain recurred and became incapacitating, and again he was admitted to the hospital. After a few days of rest, encouragement and strong reassurance, and while taking alkalis and frequent feedings, his symptoms again subsided.

At this point, he was intubated with a balloon attached to a kymograph. Gastric motor activity of an average type was recorded until suddenly an interview was engaged in in which the patient was asked why he had failed to meet his mother's ambitions and whether or not he felt that her sacrifices in his behalf had been justified. Almost immediately, gastric contractile activity became enhanced. He showed no evidence of tension or "nervousness" at first. He gave a restrained, well-organized and forceful justification of his life. As the account proceeded, however, his voice became stronger, and he became restless and tense, and the gastric contractions were associated with localized epigastric pain. The interview was allowed to continue for one hour and 30 minutes, when he was given 0.3 gm. of sodium amytal intravenously. At this point, gastric contractions stopped abruptly. His pain was promptly relieved, and his entire manner was altered. He clung weeping and sobbing to the examiner's hand, saying "I've tried so hard, so hard." He said that he finally felt relaxed, and was weeping with relief. After 27 minutes of freedom from pain, and while still under the influence of sodium amytal, a second interview was begun in which it was suggested that his change of name, his marriage to a Roman Catholic and his association with a gentile firm might represent an attempt to escape from identification with Judaism. Again his manner became restrained, his flow of conversation even and forceful. Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful.

Comment. These experiments on subjects with peptic ulcer in which painful gastric hyperfunction was induced or interrupted by appropriate manipulation of the situation established fairly clearly a relationship between the gastric disturbance and the attitudes and emotions of the subjects. They indicate that these individuals react habitually to stress with an acceleration of gastric function. They do not prove that peptic ulcer is caused by such sustained gastric hyperfunction, but they support this view. Further data were adduced from study of a fistulous human subject who happened also to have a peptic ulcer.

Case 4. A 67 year old Merchant Marine tug boat chief engineer developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital. He had noted weakness and vague epigastric discomfort but he had had no history of pain suggestive of peptic ulcer except for a brief episode 30 years before which lasted only a few weeks. Roentgen-ray examination, however,

demonstrated an ulcer with gross distortion of the duodenal cap. The stomach was dilated and emptying greatly delayed. Free acid in the gastric juice was 15 and total 38. Stools were negative for occult blood but red cells in the peripheral blood numbered only 3.4 million with 11.5 gm. hemoglobin. An exploratory operation confirmed

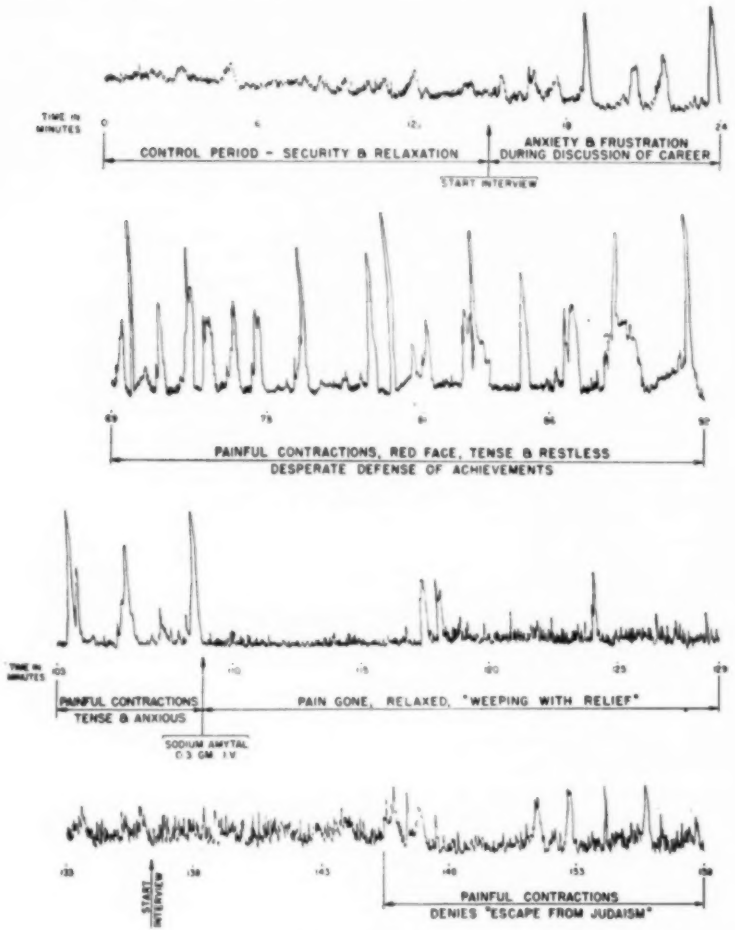

FIG. 5. Changes in motor activity in a subject with peptic ulcer (case 3) during an interview concerning significant personal conflicts.

the presence of the obstructive ulcer in the region of the duodenal cap. A posterior gastroenterostomy was performed to relieve the obstruction and post operatively a Miller-Abbott tube was left in place. The latter apparently damaged the esophagus in some way because a progressive narrowing with final occlusion of the esophagus oc-

curred over a period of three weeks. Because of the esophageal stricture a gastrostomy was done. The stoma measured approximately 5 cm. in diameter and through it herniated parts of a few engorged gastric rugae. It was accordingly possible to study this subject in the same manner in which experimental observations were made on Tom and published in detail elsewhere.[8]

The experiment was carried out 13 hours after the last feeding and with the subject reclining comfortably on a couch. The gastric mucosa was continuously observed under standard lighting conditions. Gastric juice was siphoned through a Levine tube and motor activity was recorded on a kymograph from an inlying inflated balloon. During approximately 45 minutes of control period the subject was lightly diverted and continuously reassured. As already noted the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale). Gastric juice was elaborated at the rate of approximately 20 c.c. every 15 minutes, was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units. Abruptly he was asked whether or not his own and his wife's ambitions had been satisfied by his becoming a tugboat engineer. His manner became serious and slightly grim, but he maintained that the work had been entirely satisfactory. He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers. His even manner continued although tension was evident by this time and he wiped a tear from each eye. He was further asked about possible conflicts with his wife. He denied conflicts but the denial was associated with additional lacrimation and within one-half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling the area of the stoma. Motor activity became intense and sustained and free acid rose to 35 units. No pain was noted.

Comment. This experiment provides direct visual confirmation of the findings detailed above in patients with peptic ulcer in whom the contemplation of relevant personal conflicts was associated with intense gastric hyperfunction and often symptoms.

Nature of the Personality Reaction. Numerous attempts have been made to explain why some individuals in a setting of significant emotional conflict develop troublesome gastric hyperfunction and perhaps peptic ulcer, while others may develop precisely the opposite changes in the stomach with hypoacidity, slow emptying and nausea and still others develop other physiologic disturbances but no evidence of gastric disorder. Analysis of the conflict situation has not been fruitful, and neither have attempts to construct a constitutional or personality profile been successful in delineating very sharply between those who develop and those who do not develop peptic ulcer. It has been more profitable to examine and characterize the way in which the individual habitually met threats and challenges in his life situation. The subject with peptic ulcer may feel passive and have strong dependent needs as has been pointed out by Alexander [11] and numerous others,[8, 12, 13] but his behavior is aggressive. He must appear master of the situation in contrast to the subject with gastric hypofunction, who readily assumes a passive rôle in human relationships.[14] The gastric hyperfunction itself implies a need to be fed and sustained, but it is an aggressive biologic response which in animals including man precedes the act of devouring. It is thus in keeping with the general behavior reaction of competitive aggression. These features have been reviewed elsewhere.[8, 10, 11] One probably could not answer in simple

terms why a human organism elects a defensive reaction pattern of gastric hyperfunction which when sustained may be self-destructive. It would be similarly impossible to attribute exclusively to either constitution, temperament or experience, the selection by a man who has felt on his face the glove of an adversary any of the several possible courses of action open to him. It has been pointed out elsewhere that he can choose pistols, sabres or boxing gloves, or he may elect to run away, to collapse at the feet of his challenger or sidestep the incident by retracting or making a joke of it.[15] Why he chooses one course rather than another depends upon a myriad of factors including his inherited tendencies, his early experiences, his cultural background, his habits and skills, etc. The significant question for present consideration is the character of the pattern which he does select and what its implications are for his health and survival.

Conclusion

The cause and mechanism of peptic ulcer are still unexplained, but a large body of experimental evidence supports the view that this disorder, in many instances at least, occurs as a sequel to disturbed gastric function in reaction to significant stresses in the life situation. The steps which support this formulation are briefly as follows:

1. The stomach in peptic ulcer is hyperfunctioning as regards engorgement, blood flow, acid production, motor activity and emptying time.
2. Gastric hyperfunction accompanied by epigastric pain of typical "ulcer" type may be induced in human subjects by exposure to situations involving significant personal conflict.
3. Such gastric hyperfunction is apparently mediated through vagus innervation, and is associated with two serious physiological hazards: (a) a lowering of the pain threshold in the stomach, and (b) increased fragility of the membrane.
4. Gastric juice kept in close contact with a minor erosion leads to further gastric hyperfunction and may result in the establishment of an ulcer.
5. In subjects with peptic ulcer gastric hyperfunction may be accentuated with the production of hyperacidity, hypermotility and pain by a vigorous discussion of significant personal problems.

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CALCAREOUS PANCREATITIS *

By Casimir A. Domzalski, Jr.,† M.D., *Detroit, Michigan*

Pancreatic calcification of all types is relatively rare. In a recent review of 10 large series of autopsy reports, Pascucci found pancreatic calcification reported in only 52 cases (0.044 per cent) of an aggregate total of 117,031 autopsies.[1] When looked for carefully, however, the incidence of pancreatic calcification rises more than a hundredfold, as was shown by Ludin, who carefully dissected each pancreas which showed heavy shadows in a postmortem roentgenogram. He found calcifications in 28 of 542 organs, an incidence of 5.3 per cent.[2]

The clinical incidence of pancreatic calcification, especially in recent years, is higher than one would be led to expect from autopsy reports. Up to the year 1946 there were 243 cases of pancreatolithiasis reported,[3] of which 15 per cent had appeared in the last 14 years. Diffuse parenchymal pancreatic calcification, a much rarer condition, had been reported only 20 times, roughly half of these in the last four years. Fourteen additional cases of the latter were reported in 1946 by Comfort and his associates.[4]

Pancreatic calcification falls naturally into three categories: (1) Calcifications in the form of stones lying free in the ducts of Wirsung and Santorini and their tributaries. Ranging in size from "gravel" to solitary stones weighing as much as 60 grams,[5] they may be mulberry-shaped or have sharp edges with a propensity for erosion either into blood vessels with gross and occasionally fatal intestinal hemorrhage,[6] or into the abdominal cavity. They are composed chiefly of calcium phosphate and carbonate, and vary in color from gray to brown depending on the amount of bile-staining which has occurred. (2) Diffuse parenchymal calcifications, distributed throughout the gland in the interstitial tissue and in the dense connective tissue which ultimately replaces most of the glandular tissue in a chronically inflamed pancreas. (3) Mixed calcification of the pancreas, featuring both parenchymal and free intraductal calcifications. While it is not possible clinically to differentiate which type is present, it is frequently possible to do so by roentgen-ray. From the standpoint of treatment such a differentiation is important, since complete relief might be expected from surgical intervention in pure calculous disease, whereas treatment should be medical in cases of diffuse calcification with pancreatic insufficiency. This insufficiency may be endocrine, in the form of diabetes mellitus, or exocrine, in the form of steatorrhea and creatorrhea, or both.

Two cases of diffuse pancreatic calcification which were seen during the past year at Queen's Hospital are reported because of their relative rarity and because several striking clinical features were common to both cases.

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Case Reports

Case 1. A 43 year old Irish-Hawaiian male was first admitted to Queen's Hospital July 12, 1945, with a chief complaint of weakness. He had diabetes and had been taking insulin "off and on" for one year. During this period he had developed a persistent diarrhea, had lost about 70 pounds, and had become very weak. He described his stools as being large and yellow, with "droplets of oil" on the surface of the water after an evacuation.

His past history included measles, mumps, and chickenpox in childhood, and pneumonia at the age of 27. The only previous gastrointestinal disturbances he had ever experienced were three bouts of severe epigastric pain many years previously, which the patient attributed to over-indulgence in alcohol. His father had had diabetes and died at the age of 54. His mother had died of a "stroke" at the age of 72. There was no other history of diabetes in the family.

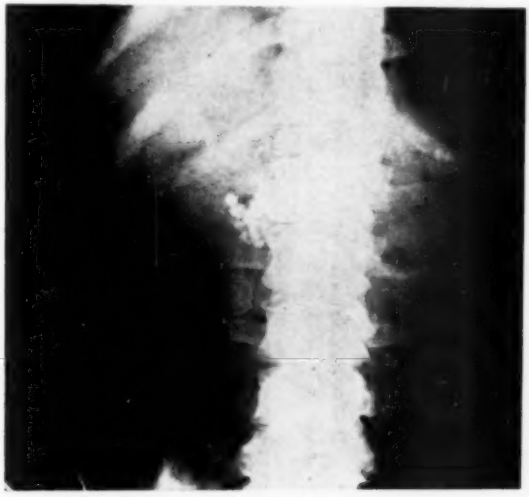

Fig. 1. Roentgen-ray of the abdomen, case 1, showing multiple calcifications in the head and tail of the pancreas.

Physical examination revealed a tall, gaunt male who appeared chronically ill. There were slight reddening and atrophy of the tongue, and tiny fissures at the corners of the mouth. The remainder of the examination was essentially negative except for evidence of rather marked weight loss. Admission blood count showed 5,180,000 erythrocytes, 13 gm. of hemoglobin, and 16,150 leukocytes, with 42 per cent polymorphonuclear leukocytes and 58 per cent lymphocytes. The urinalysis was negative and the blood sugar was 158 mg. per cent. A stool examination showed a large number of striated muscle fibers and 16 per cent of the dry weight was fat.

A barium enema revealed a normal colon but the roentgenologist noted a large accumulation of calcific deposits in the pancreas. A lateral film of the abdomen confirmed the location of the calcifications. An oral cholecystogram demonstrated a normal gall-bladder. An upper gastrointestinal roentgen-ray study was essentially negative except for a slight compression of the descending and transverse portions of the duodenal loop from without, apparently by the head and body of the pancreas.

This patient's diabetes proved almost impossible to control. His ravenous appetite necessitated a rapid increase in his caloric intake from 1,900 calories a day to 2,500 calories a day. His urine was tested for sugar before each meal and was utterly unpredictable, varying from negative to four-plus for the same meal and same insulin dosage on successive days. Insulin dosage was arbitrarily fixed at 60 units of protamine zinc insulin each morning, after many fruitless adjustments. He was given Syntropan for the epigastric discomfort of which he complained. He had not mentioned this pain on admission, but admitted that he had had it for quite some time. It was not relieved by Syntropan and the medication was discontinued. He was given pancreatin, five grains three times daily, and this dosage was doubled on the eighth day. The diarrhea subsided to one or two stools daily,

FIG. 2. Lateral film of the abdomen, case 1, demonstrating the pancreatic calcifications immediately anterior to the spine.

but these were still bulky and fatty. By the fifteenth day, the patient had gained five pounds, felt much better, and wished to be discharged although his diabetes was still uncontrolled. He was taught how to test his urine for sugar and was discharged with a supply of insulin.

Second Admission. The patient returned to the hospital December 3, 1945, again complaining of weakness and weight loss. His weight had fallen to 125 pounds and he had developed a chronic cough. Physical examination revealed much the same picture as at the time of the first admission. The blood count showed 5,100,000 erythrocytes, 10.6 gm. of hemoglobin, and 13,200 leukocytes, with 73 per cent polymorphonuclear leukocytes and 25 per cent lymphocytes, 1 eosinophile, and 1 monocyte. Urinalysis was negative except for a four-plus sugar reaction. The blood

calcium was 9.4 mg. per cent and the blood phosphorus was 2.8 mg. per cent. The blood Laughlen test was negative. Blood amylase was 10 per cent (Fennel's method: 10 per cent to 35 per cent is normal), and the urinary amylase was 2 per cent. A roentgenogram of the abdomen again demonstrated the multiple pancreatic calcifications, and a chest film showed bronchiectasis of the left lower lobe with an associated pleural reaction obliterating the corresponding diaphragm.

Carbohydrate metabolism was still erratic and great difficulty was encountered in stabilizing his diabetes. As he gained weight, however, his insulin requirement gradually decreased from 110 to 40 units of insulin daily. He was given kaopectate and at times paregoric for his diarrhea, as well as pancreatin, one gram three times daily. Amphogel was effective in relieving the sporadic epigastric pain of which he complained. He improved slowly, the cough disappeared, and his weight increased to 146 pounds. He was discharged April 18, 1946.

Third Admission. The patient was readmitted July 10, 1946, with a chief complaint of hemoptysis. He had felt well until about 10 days prior to admission, when he contracted a "cold." He developed a cough productive of yellow sputum which later became blood-tinged. A few moist râles at the left apex were the only new finding on physical examination. The blood count was normal except for a slight leukocytosis (11,200), with a normal differential, and the urinalysis was negative except for a four-plus sugar reaction. The blood sugar was 196 mg. per cent. The sputum contained large numbers of tubercle bacilli, and a chest film demonstrated a small reticulated infiltration in the upper lobe of the right lung. A right phrenicotomy was done September 11, 1946, and one week later the sputum was negative for acid-fast bacilli on three successive examinations. His diabetes remained difficult to control and a day-to-day variation of the insulin dosage was necessary. Steatorrhea was still present but responded fairly well to pancreatin and kaopectate, and his weight increased from 134 to 144 pounds. He was transferred to a sanatorium September 28, 1946.

Case 2. A 39 year old white male applied for a position as chef at Queen's Hospital in August, 1946. The preëmployment chest roentgenogram showed a moderately large pulmonary infiltration in the apical portion of the left lower lobe, probably tuberculous. He was admitted to the isolation unit of the hospital and put on a regimen of strict bed rest. His history revealed that he had had an increasingly productive cough for about three weeks, but no other symptoms. Physical examination was entirely negative. His blood pressure was 120 mm. Hg systolic over 78 diastolic.

There was nothing of note in his past history up to about two years before admission, at which time he had suffered a marked weight loss (approximately 70 pounds in two months), attributed by the patient to the fact that he had just had most of his teeth extracted. However, a Selective Service examination revealed that he had diabetes mellitus. He was rejected and no treatment was undertaken by the patient. Eighteen months prior to admission he had been hospitalized in Los Angeles with a bilateral pneumonia and during his stay in the hospital treatment of his diabetes was carried out. He was taking 40 units of protamine zinc insulin each morning at the time of discharge, and continued to take it regularly until his admission to Queen's Hospital. Chest roentgen-ray at the time of discharge was said to show complete resolution of the pneumonia. A short time before the patient developed this pneumonia, a close personal friend had died of pulmonary tuberculosis. There was no family history of diabetes or tuberculosis.

The sputum was positive for acid-fast bacilli. The sedimentation rate was not elevated. The blood count was normal and the urinalysis was negative. He was put on a daily dose of 55 units of protamine zinc insulin. His appetite seemed to increase steadily, but on the sixtieth hospital day his weight was the same as on ad-

mission, although his caloric intake had been gradually increased to 3,000 calories daily. It was noted during this period that the patient's stools were consistently bulky, pale, and extremely malodorous. He did not complain of diarrhea at any time. An analysis of the stool showed it to be 46 per cent fat (dry weight). Pancreatic steatorrhea was suspected and a roentgen-ray of the abdomen was obtained. This showed extensive calcification throughout the entire pancreas. There was complete failure of visualization of the gall-bladder on oral cholecystography, which was interpreted as demonstrating marked impairment of function of the gall-bladder. There was no roentgen evidence of cholelithiasis. After the patient had received one gram of pancreatin daily for 10 days, a second stool analysis showed that 54 per cent of the dry weight was fat. During the third month of hospitalization this patient was on a diet of 3,250 calories a day, and his insulin requirement had increased to 70 units daily. His weight had increased from 138 to 145 pounds.

At the end of the third month he became despondent over family difficulties and his appetite waned, resulting in a five-pound weight loss. He became moody and intractable and insisted on being released from the hospital. He was discharged against advice December 27, 1946. No insulin was furnished him at discharge.

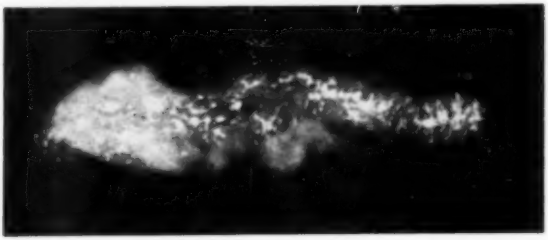

FIG. 3. Postmortem roentgen-ray of pancreas, case 2, showing replacement of practically the entire gland by calcific deposits.

He was seen by various hospital personnel during the next few days and it was evident that he was drinking heavily. He was readmitted the fourth day after discharge in coma. He appeared pale, moderately cyanotic, and was perspiring profusely. He had had a very large involuntary evacuation. His temperature was 101° F., pulse 90 per minute, and blood pressure 180 systolic over 104 diastolic. The respirations were rapid, deep, and rattling in character. Examination revealed soft eyeballs, loss of all muscle tone, coarse rhonchi throughout the chest, hyperactive heart sounds, and absence of all reflexes, including the corneals. Urinalysis showed no sugar and the blood sugar was 28 mg. per cent. The blood count showed 4,760,000 erythrocytes, 12.2 gm. of hemoglobin, and 38,000 leukocytes, with 91 per cent polymorphonuclears and 9 per cent lymphocytes.

Massive amounts of glucose were given intravenously; within two hours the blood sugar was 92 mg. per cent and within five hours the urine showed a 3-plus sugar reaction. He did not improve and at the end of 12 hours his temperature was 103° and acute pulmonary edema developed. The pulse was 160 per minute and copious amounts of froth poured from his mouth and nose. A venesection was done and Ouabain was given intravenously with dramatic improvement. The following morning the chest was fairly clear and the pulse was down to 120 per minute. He remained in coma in spite of blood sugar levels reaching as high as 600 mg. per cent. There was constant urinary spillage of sugar but acetone bodies did not appear. Moderate doses of regular insulin were given. A lumbar puncture on the third day

revealed entirely normal spinal fluid, and an electrocardiogram on the fourth day was essentially normal except for tachycardia. A serum amylase determination on the fourth day was normal, and the serum calcium was 11.4 mg. per cent. Although his white count slowly fell to 18,000, his fever progressively mounted and he died on the fifth day without having regained consciousness. Penicillin, 50,000 units, had been given intramuscularly every two hours since admission. The clinical diagnoses were insulin shock of irreversible type, such as occurs in about 1 per cent of all patients given insulin shock therapy,[7] and bilateral bronchopneumonia.

At autopsy, the pancreas weighed 80 grams and felt like a bag of pebbles. On section, multiple irregular calcific nodules were found throughout, the largest measuring about 0.5 cm. across. The entire gland seemed to consist of dense connective tissue so that no parenchyma could be identified and the ducts could not be made out. Histologic study showed it to be densely fibrotic connective tissue containing only a few islands of Langerhans, a few duct-like structures, and an occasional small nest of distorted acinar cells. The many calcifications seemed to be deposited around what appeared to be areas of old fat necrosis. The islets which remained were small and in the process of being obliterated by the fibrotic process. The liver weighed 1,750 grams and was firm and smooth, with moderate passive congestion, but no fatty infiltration was detected. The gall-bladder appeared normal, emptied easily, and contained no stones. There was no evidence of fat necrosis in the mesentery or omentum. Three small superficial ulcers, which proved to be tuberculous on histologic examination, were found in the mucosa of the ileum near the ileo-cecal valve. Each lung weighed 720 grams and showed mild congestion and edema, with patchy atelectasis and lobular pneumonia. A well walled-off tuberculous abscess, 2 cm. in diameter, was present in the left apex together with a cicatrizing pleural scar. A similar lesion was found at the hilum of the left lung.

Discussion

The outstanding clinical features of these two cases of pancreatic calcification were: (1) steatorrhea with marked weight loss, (2) severe, and in one case intractable, diabetes, and (3) complicating pulmonary tuberculosis. It has been generally observed that steatorrhea occurs in only about one-half of all cases of calcareous pancreatitis. It was a prominent feature in both cases reported, although only the first patient actually complained of diarrhea. Pancreatic insufficiency could reasonably be expected from the relatively marked destruction of glandular tissue that was shown by the roentgen-ray, although disturbances of pancreatic function have been absent in about 10 per cent of the reported cases of pancreatic calcification.[4]

Diabetes mellitus, latent or active, is said to occur in about 50 per cent of all cases of pancreatic calcification.[8] This is a much higher incidence of diabetes than occurs when pancreatic damage is due to obstruction of the ducts by a pancreatic calculus. It is well known that when stones obstruct the pancreatic ducts, destruction of the acinar tissue is early, rapid, and quite complete, but the islands of Langerhans survive until very late in the process. Exocrine failure precedes endocrine failure of the pancreas when pancreatic destruction is due to ductal obstruction. No better illustration of this could be cited than the fact that Banting and Best were launched on the investigation which ultimately led to the discovery of insulin [9] by Barron's autopsy report on a patient who had had a pancreatic stone.[10] The pancreas of this

patient showed total atrophy of the acini with preservation of the islets of Langerhans.

However, this does not hold true in case of diffuse parenchymal calcification of the pancreas, and even the reverse may occur: the islets are sometimes destroyed first. The diabetes may appear even before calcareous pancreatitis develops. This occurred in two of Pasternack's cases [8] and in both of our cases. This is not at all difficult to understand when the two underlying pathological processes are separately analyzed. Ductal stones destroy acinar tissue by simple back-pressure and retrograde inflammation secondary to stasis. In contrast, diffuse parenchymal calcification occurs first in the interstitial tissue. This tissue is involved in both acute hemorrhagic pancreatitis, and in acute interstitial pancreatitis as described by Elman [11] and others. The latter type of pancreatitis often masquerades as brief episodes of gastrointestinal upset, with epigastric or generalized abdominal pain, nausea, vomiting, and sometimes diarrhea. The diagnosis rests mainly on the characteristic elevations in the serum amylase and lipase, and is helped when there is pain which radiates to the back or to the left costovertebral angle. Acute interstitial pancreatitis may also be misinterpreted as acute alcoholic gastritis, which is probably what occurred in case 1. He had had three previous bouts of severe epigastric pain accompanied by vomiting, and had attributed them to alcoholic excesses.

Acute pancreatitis of the hemorrhagic type undoubtedly plays an important rôle in the pathogenesis of calcareous pancreatitis. The fat necrosis which is found in acute hemorrhagic pancreatitis is due to a splitting of neutral fat into fatty acids and glycerine by lipase which escapes from the pancreas into the tissues. Insoluble soaps are then formed by the combination of the liberated fatty acids with calcium. The glycerine is absorbed. Edmondson and Fields [12] have demonstrated a moderate fall in the serum calcium of patients with acute pancreatic necrosis, and large amounts of calcium in the pancreatic lesions. A depression of the serum calcium has been reported in several cases of calcareous pancreatitis and occurred in case 2. At autopsy, the pancreatic calcifications were found to be centered around what were probably areas of old fat necrosis.

Comfort et al.[4] have recently demonstrated in a fairly large series of cases that both interstitial and hemorrhagic pancreatitis occur as the acute phases of what they term chronic relapsing pancreatitis. Diffuse calcification developed in 14 of their 29 cases. Chronic relapsing pancreatitis is a disease characterized by remissions and acute exacerbations of either interstitial or sublethal hemorrhagic pancreatitis. Whether both types of acute inflammation occur in the same patient at different times has not been established, but either type has been definitely shown capable of producing chronic pancreatitis with any or all of its sequelae of steatorrhea, diabetes, and calcification. Disturbances in pancreatic function may be transitory, demonstrable only during the acute attack, or permanent. Complete pancreatic failure may be unaccompanied by calcification, and contrariwise, calcification without any

metabolic disturbances has been reported. Calcification may rarely develop painlessly (only one case in Comfort's series). Case 2 was evidently in this category.

It should, of course, be borne in mind that acute interstitial and acute hemorrhagic pancreatitis are distinct entities and may occur only once in the lifetime of an individual. That the latter and chronic relapsing pancreatitis are not identical is highlighted by the fact that diabetes has been found only rarely (2 per cent) to follow acute hemorrhagic pancreatitis,[12] whereas it occurs in 50 per cent or more of all cases of calcareous pancreatitis.

Complicating biliary disease is reported to be fairly common in almost all forms of pancreatic disease. A normal cholecystogram was obtained in the first case, and although abnormal function was reported in the second case, no structural abnormality was discovered at autopsy. Degenerative fatty infiltration of the liver producing a palpably enlarged liver occurs in some cases of chronic pancreatitis, the "pancreato-hepatic syndrome," [14] most probably due to a deficiency in lipocaic, the pancreatic hormone which regulates the deposition of fat in the liver cells. Hepatomegaly was not present in the first case, and the liver was essentially normal on histologic study in the second case.

A history of alcoholism has often been cited as a salient feature in pancreatic inflammatory disease. It was regarded, however, as a merely coincidental finding until the accumulation of recent evidence, which has pointed to alcohol as at least a frequent precipitating agent if not actually of etiological importance. Carter [15] found tremendously elevated serum amylase values in 11 alcoholic patients with acute abdominal symptoms. Four of the patients were operated upon and acute interstitial pancreatitis was found. Alcohol definitely precipitated acute attacks in 14 per cent of Comfort's cases of chronic relapsing pancreatitis, and 59 per cent of his patients were users of alcohol. This has borne out the observations of earlier writers such as Weiner and Tennant,[16] Myers and Keefer,[17] and Clark.[18] Our first patient was a constant heavy user of alcohol, and the second patient was a sporadically heavy drinker. In a study of 4,000 autopsies, Weiner and Tennant concluded that pancreatic disease is 40 to 50 times as frequent among alcoholics as among non-alcoholics.

Patients with calcifying disease of the pancreas are predisposed to pulmonary complications, and both of our cases developed pulmonary tuberculosis. Two of Pasternack's cases and one of Snell and Comfort's also had pulmonary tuberculosis. Other pulmonary complications, such as bronchopneumonia, abscess, and gangrene have been reported. It is interesting to speculate as to whether or not the metaplasia of the bronchial epithelium resulting in these patients from the loss of vitamin A in the fatty stools [13] is an important factor in predisposing them to pulmonary infections. It appears that the pancreatic insufficiency not only predisposes to pulmonary infection but also has quite a direct bearing on the patient's response to it. The first patient had intractable diabetes and showed relatively little resistance to the

tubercle bacillus. He has been followed since his transfer to the sanatorium, and generalized pulmonary spread of the tuberculosis is developing. The second patient had easily controlled diabetes and his pulmonary lesion was well walled-off.

There is little reason to suppose that the calcifying pancreatitis is tuberculous in nature. In both of our patients the diabetes antedated the pulmonary tuberculosis by approximately two years, and in the first case steatorrhea definitely preceded the pulmonary lesion by about 18 months. Autopsy reports on cases of pancreatic calcification, even when complicated by pulmonary tuberculosis, do not mention (except for one case)[2] the finding of tuberculous lesions in the pancreas.

The treatment of chronic calcifying pancreatitis involves both medical and surgical procedures. Diabetes and steatorrhea are medical problems and the former needs no discussion here. Steatorrhea will usually respond to dietary measures and replacement therapy with pancreatic enzymes. A low fat diet is indicated, not only because these patients are often intolerant of fatty foods, but also because such a diet has been shown both experimentally and clinically to produce the greatest stimulation of pancreatic production of amylase and trypsin. Conversely, a high fat diet definitely suppresses secretion of pancreatic ferments. Pancreatin was moderately helpful in correcting the troublesome fatty diarrhea in the first case, and exerted no appreciable effect on the character of the stools of the second patient during the short time it was used. It should be stated, however, that the doses of pancreatin given to these two patients were woefully inadequate. To be effective in pancreatogenous diarrhea, 10 to 30 grams of pancreatin should be given daily.[14] The addition to the diet of protein-digests and amino acid preparations in which the work of pancreatic enzymes has already been done in vitro has recently added an important therapeutic measure to the management of this enzyme-deficiency state.[11] Because of the faulty absorption of vitamins, especially those of the fat-soluble group, the diet should be supplemented by massive doses of these substances.

Acute exacerbations of pancreatitis, whether interstitial or hemorrhagic in type, should be managed medically, according to a growing consensus. The pain, which varies in character and intensity depending on the nature of the underlying process, usually requires opiates but occasionally responds to ephedrin. Parenteral replacement of fluids lost by vomiting and diarrhea is essential, and the usual measures are employed to combat distention and shock when these occur.

Surgical intervention is clearly indicated when ductal stones are demonstrated, either alone or with parenchymal calcifications when there is reason to believe that pain or achylia will be relieved by the removal of the stones. Chronic obstruction of the duodenum calls for a short-circuiting operation such as gastroenterostomy, or for a partial pancreatectomy. Encroachment on the bile duct by the enlarged pancreas with the production of chronic, persistent pain is relieved by either internal biliary drainage (anastomosis of the

common duct to the stomach, duodenum, or jejunum), or external drainage by means of choledochostomy or cholecystostomy. Pain and pressure symptoms arising from pancreatic cysts which sometimes occur in chronic pancreatitis are relieved by marsupialization or internal drainage of the cysts into the small intestines. When intractable pancreatic pain is not demonstrably due to any of the above mentioned factors, more radical surgery may be necessary. Successful subtotal pancreatectomy with complete relief of pain in a small number of such patients has been reported during the past year.[4, 19]

SUMMARY

1. Two cases of chronic pancreatitis with calcification, diabetes, and steatorrhea are reported.

2. Both cases were complicated by pulmonary tuberculosis.

3. The incidence, classification, pathogenesis, clinical features, and treatment of calcifying pancreatitis are briefly discussed.

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DISCUSSION BY ALFRED S. HARTWELL, M. D.:

No paper on calcareous pancreatitis should fail to mention the interest with which for 40 years Dr. Joseph H. Pratt has studied pancreatitis. In recent years he has been interested in the secretin test of pancreatic function. He obtained from Agren and Lagerlöf [1] some purified crystalline secretin and administered it intravenously to patients with actual, and also suspected, pancreatic disease. It will be recalled that secretin was first shown to exist by Bayliss and Starling [2] in 1902. This substance, which is extracted from small intestinal mucosa, when injected intravenously causes a very large volume of alkaline pancreatic juice to be excreted by the pancreas. When constant duodenal and gastric drainage is used, so that the gastric contents are kept separate from the duodenal contents, one can determine with considerable accuracy the volume of pancreatic juice which a given amount of secretin will cause to be excreted. The intubation of the duodenum and constant suction of it with controlled negative pressure is a time-consuming procedure and is largely restricted to centers where research is carried out. It would have been of interest, however, to have done secretin tests of pancreatic function in these two cases. The reader is referred to the discussion of pancreatic disease by Dr. Pratt in the Frank Billings Lecture of 1942.[3]

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A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS *

By GEORGE N. PAPANICOLAOU, M.D., *New York, N. Y.*

IN 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

Now that the method has been tested by general use over a number of years our knowledge has been advanced to a point where we are able to differentiate with a fair degree of accuracy between lesions affecting different parts of the female genital tract, as well as between various cell types and smear patterns. We are now in a position to make a clearer distinction between the squamous cell type carcinomas of the cervix and the adenocarcinomas of the endometrium, in which the abnormal cells are of the glandular type. It is even possible at times to make a differentiation between an adenocarcinoma of the endometrium and one of the cervix, in which the abnormal cells are of the endocervical type.

Metaplasias of the endocervix and of the endometrium may also be recognized occasionally when clusters of endocervical or endometrial cells are present, in which some of the cells show a change toward the parabasal squamous type. In metaplasia of the endometrium one often encounters rosette-like clusters of cells in which there is marked enlargement and vacuolization of some of the more peripherally located cells. Endocervical or endometrial polypoid hyperplasias may be revealed by small polypoid fragments of the endocervical or endometrial mucosa found in endocervical or endometrial smears.

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From Cornell University Medical College.

Ovarian carcinomas can be detected in the smears when there is metastasis to the tubes or the uterus. The cytology of metastatic cystadenocarcinomas of the ovary is usually sufficiently characteristic to permit their distinction from primary adenocarcinomas of the uterus.

Recently we had occasion to study two cases * in which numerous cystadenocarcinoma cells were found in smears aspirated from the endometrial cavity,† whereas no such cells were found in the vaginal smear taken from one of the two cases. In neither of these was there any evidence of metastasis to either the uterus or the tubes. However, much ascitic fluid was present in both cases, and it is possible that such fluid, containing malignant cells, carried them through the tubes into the uterine cavity.

In cases of ovarian carcinomas with exudation of fluid into the peritoneal cavity malignant cells may be recovered in the centrifuged exudate.

Tubal carcinomas can be diagnosed by means of smears, but their origin cannot be well established unless fluid is drawn directly from the tube.‡

In the cervical carcinomas some distinctive smear patterns may be recognized.

In advanced squamous cell carcinomas of the cervix there is, as a rule, a great variety of atypical cells showing marked structural and nuclear abnormalities. Some of the cells acquire bizarre forms. Clusters of malignant cells are frequently encountered and show crowding, anisokaryosis, disorientation, engulfment and other abnormal features.

In carcinomas of the cervix which are still in an early intraepithelial stage the cytologic changes are less marked. The nuclei show distinct abnormal features such as enlargement, hyperchromasia, anisokaryosis, bi- or multinucleation, etc., but the malignant cells do not exhibit the extreme deviations from the normal types from which they originate, as they do in advanced cases of malignancy. Furthermore, in the early carcinomas the malignant cells usually appear singly or in small groups in contrast to advanced carcinomas, in which larger and more crowded groups are present.

* These cases were referred to us by Dr. Sophia Kleegman.

† The method of aspiration is described by Dr. Kleegman as follows:

The vagina and cervix are cleansed with Tincture of Merthiolate and the anterior lip of the cervix grasped with a tenaculum. An antrum cannula attached to an empty, closed 5 c.c. syringe is then inserted directly into the endometrial cavity, approximately .5 inch from the fundus. If the internal os is very tight, it may be necessary to pass a number 9 or number 10 Hank dilator through the internal os. Usually, dilatation is not necessary. With the antrum cannula in the endometrial cavity, the plunger of the syringe is withdrawn, creating suction. The syringe is then detached from the cannula, closed, and again attached, suction is applied for a second and then a third time. This will give sufficient material to make an adequate examination. The cannula is then withdrawn from the uterus, and the contents are expelled on the end of a glass slide by blowing air through the cannula. The material is spread over the lower inch of the slide, and dropped promptly into the alcohol-ether solution. Not infrequently, a small strip of endometrium will also be aspirated in this way, comparable to the amount of material obtained with an endometrial biopsy curet. If desired, this can be fixed and prepared for a pathological examination.

‡ Thus far we have had only one case, referred to us by Dr. Virginia Pierce of Memorial Hospital, in which fluid was obtained from each one of the tubes separately. A pre-operative diagnosis of carcinoma of the left tube was made possible in this case by the cytologic examination of the two specimens.

The term "dyskaryosis" has been adopted to designate these early cytologic changes, which are centered in the nucleus. Several types of dyskaryosis may be distinguished on the basis of a predominance of one or more distinctive cell types.

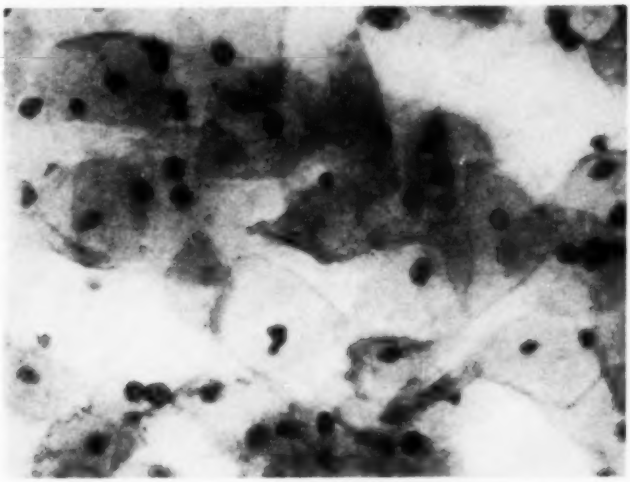

FIG. 1, *a*. Superficial squamous cells. Normal. × 400.

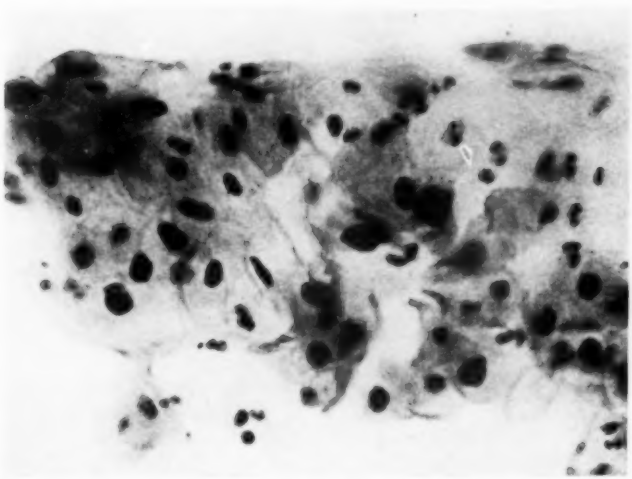

FIG. 1, *b*. Superficial squamous cells characteristic of superficial cell dyskaryosis. × 400.

We speak of a "superficial cell dyskaryosis" [1] when the prevailing abnormal cells are of the superficial squamous type (figures 1a, 1b). Some of these abnormal cells may be cornified and, as a rule, a relatively high degree of cornification is associated with this condition, which is the most commonly met with of all the forms of dyskaryosis.

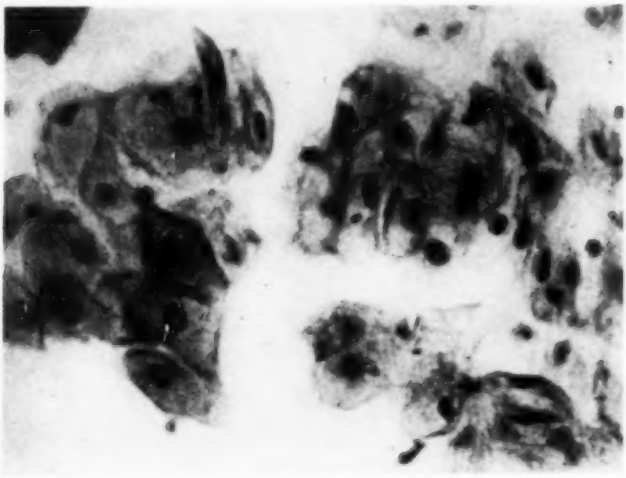

FIG. 2, *a*. Intermediate (navicular) cells. Normal. × 400.

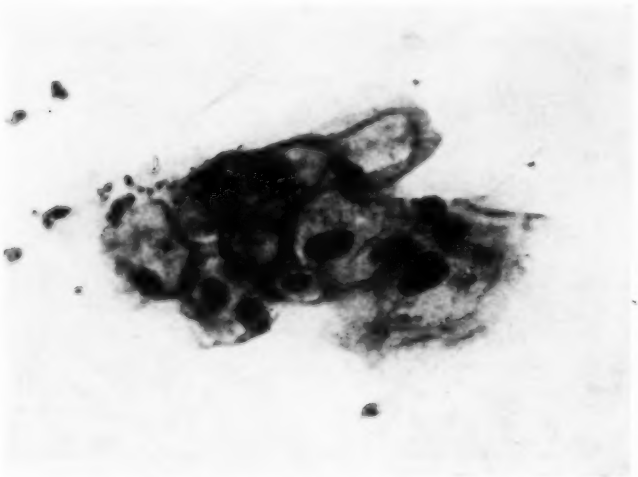

FIG. 2, *b*. Intermediate (navicular) cells characteristic of intermediate cell dyskaryosis. × 400.

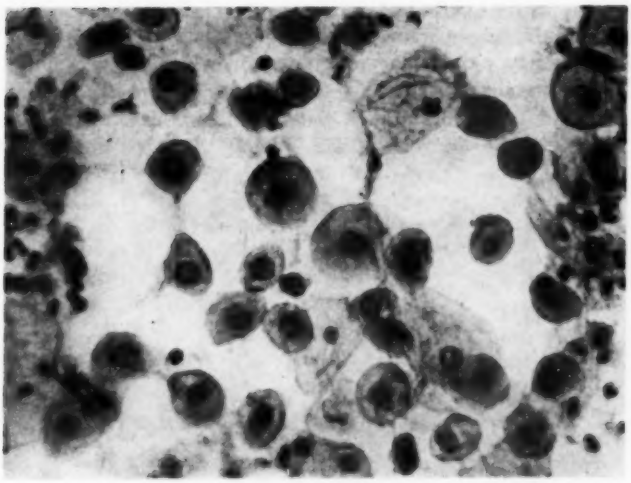

FIG. 3, *a*. Cervical parabasal cells. Normal. × 400.

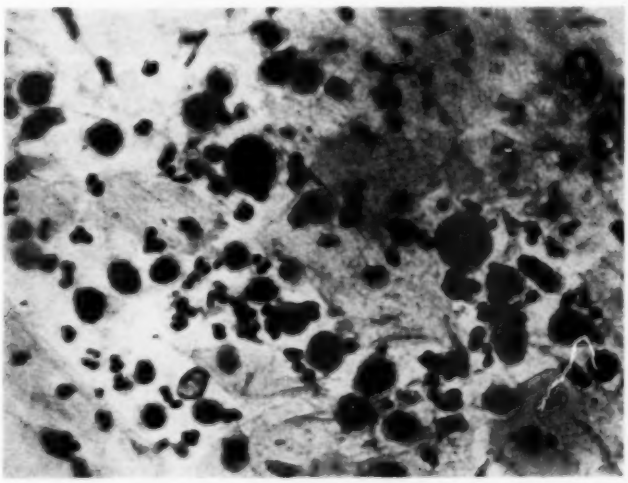

FIG. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis. × 400.

The term "intermediate or navicular cell dyskaryosis" is used to indicate the prevalence of abnormal cells deriving from the intermediate or navicular zone (figures 2a, 2b). This type of dyskaryosis is rather rare and thus far we have had only two clear-cut cases of it.

A third type, the "parabasal cell dyskaryosis", is characterized by a preponderance of abnormal parabasal cells (figures 3a, 3b).

Still another type of dyskaryosis is that in which the prevailing abnormal cells are of endocervical origin (figures 4a, 4b).

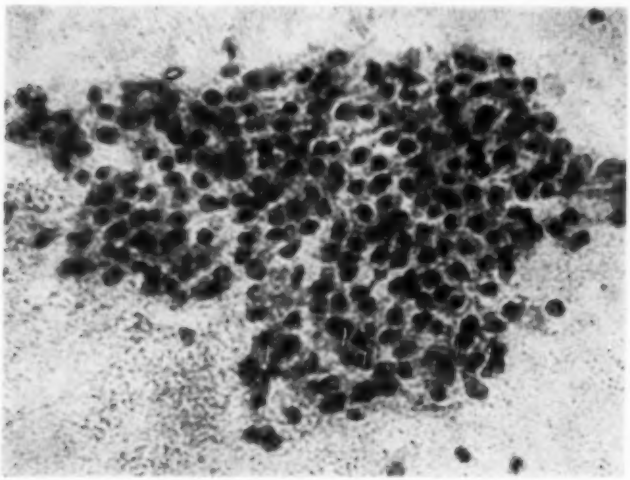

FIG. 4, *a*. Endocervical cells. Normal. × 400.

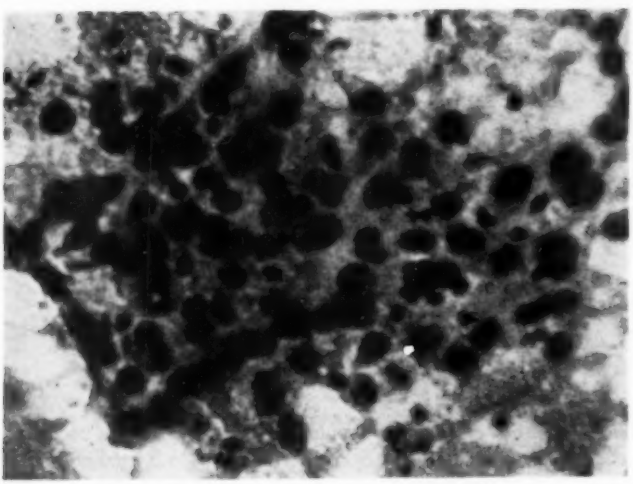

FIG. 4, *b*. Endocervical cells characteristic of endocervical cell dyskaryosis. × 400.

The significance and the prognostic value of these different patterns which seem to correspond to the earliest stages of malignant lesions of the cervix are not yet properly understood, nor will they be until an exhaustive correlative study of cytologic and pathologic findings has been made. What tends to complicate the picture is that not infrequently cells representing various dyskaryosis types are found to be intermixed.

Cases have also been noted in which the dyskaryotic cytology was found to coexist with that of an invasive squamous cell carcinoma. In some of these cases transitional cell forms linking the two cytologic patterns have also been observed. Should this fact be interpreted as indicating that the one would eventually develop into the other? An affirmative answer would be only an assumption, since in none of these cases have we had any positive evidence of a progressive change from one pattern to the other. On the other hand, in at least one case of superficial cell dyskaryosis, which we followed over a period of 10 years, this condition proved to be reversible.

Our observations in this field of early malignant lesions of the cervix and of their corresponding cytologic patterns are still fragmentary. It is not always possible to obtain a confirmation of smear findings by biopsy. Instances are not uncommon in which multiple biopsies have been necessary to prove the presence of an early carcinoma. In a recent case, only one out of eight biopsies taken offered positive evidence of a carcinoma in situ. Even after complete hysterectomy it is not possible to verify the absence of a malignant lesion without a serial microscopic study of the cervix, which is impracticable as a routine procedure.

Another difficulty is the lack of general agreement among pathologists as to the criteria of a carcinoma in situ. It sometimes happens that a section showing a marked degree of epidermidalization may be interpreted in some laboratories as carcinoma in situ. All these reasons make it very difficult to evaluate accurately the incidence of carcinoma in cases in which a dyskaryosis smear pattern has been observed.

In view of the fact that at present no general agreement can be reached as to the criteria of carcinomas in situ, their separation into two groups appears to be justifiable. One of the two groups would include cases characterized by clean-cut criteria that would be generally acceptable and that would satisfy the most exacting standards; the other would consist of cases in which the criteria fall below such standards and in which there may be disagreement as to the true nature of the lesion.

The term "carcinoma in situ" or "intraepithelial carcinoma" should be retained for the first group, whereas the second one should be designated by a new term which would not necessarily suggest malignancy. The term "pre-cancerous", which has been used extensively for ambiguous lesions, would be rather objectionable, as it implies an inevitable malignant transformation. In a recent discussion of this point the term "dysplasia" * was

* This term was suggested by Dr. William B. Ober of the National Cancer Institute at Bethesda, Maryland.

proposed to specify such cytologic changes as would be suggestive of but not conclusive for malignancy.

The acceptance of a new term to designate a distinct group which would include all cases that are questionable or apt to be contested from the pathological standpoint would greatly contribute to a more satisfactory and less controversial evaluation of early malignant lesions. Moreover, the term "dysplasia", like that of dyskaryosis, may be advantageously combined with other terms specifying the site of the lesion and the predominating cell type, thus adding greatly to its descriptive value.

In the early period of our studies only vaginal aspiration smears were used. We now consider the vaginal smear alone rather inadequate, and in addition to it, we request an endocervical aspiration smear and a direct cotton swab or spatula smear. In cases in which an adenocarcinoma of the fundus or a carcinoma of the ovary is suspected, an endometrial aspiration smear is of great value.

In some laboratories only a swab or spatula smear is used. Our experience is that with such a limitation one may often miss carcinomas of the uterine fundus, of the tubes and of the ovaries, or even of the cervix, if the site of the malignant lesion happens to be outside the area covered by the swab or spatula.

Our technical procedures related to fixation and staining are now fairly well standardized. We still adhere to the principle of an immediate fixation in alcohol-ether and of an adequate staining technic which brings out the nuclear structure, and insures transparency of the cytoplasm and a good differentiation between the basophilic and acidophilic cells.

With regard to the use of the smear technic in the diagnosis of malignant neoplasms of organs other than those of the female genital tract, it appears that a higher level of standardization and accuracy has been achieved in the diagnosis of carcinomas of the respiratory tract, by the cytologic examination of sputum and of bronchial aspirates and washings. This is a field in which considerable progress has been made through the work of previous investigators. By using cytologic criteria we now feel that it is possible not only to detect the presence of carcinoma in the lungs, but also to recognize a number of distinct types.

The squamous cell type is probably the one presenting the most characteristic cytologic picture. The presence of cells showing squamous metaplasia and a strong acidophilic, or rather, orangeophilic reaction, in association with marked nuclear abnormalities, helps toward an easier and safer recognition of neoplasms of this type.

In undifferentiated bronchogenic carcinomas the malignant cells appear in clusters showing an irregular pattern and nuclear abnormalities such as enlargement, anisokaryosis, prominence of the chromatin and of the nucleoli, and other changes characteristic of malignancy.

Carcinomas of the oat celled type can be surely identified by the small size

of the malignant cells, their extreme hyperchromasia, the anisokaryosis and the scantiness of the cytoplasm.

Adenocarcinomas may be recognized as such when the cells are well preserved and reveal their glandular origin. Exfoliated cells of this type frequently show an eccentric position of the nucleus and vacuolization of the cytoplasm. The cells are often grouped in rosette-like clusters.

Malignant neoplasms of lymphoid origin, such as Hodgkin's disease or reticulum-cell sarcoma, also present a distinct cytologic picture. The cells appear, as a rule, singly, and although relatively small, they can be safely identified by the coarse granulation, hyperchromasia, and fragmentation of their nuclei. An excess of lymphocytes was observed in some cases of lymphatic leukemia. In general, it may be stated that large clusters of lymphocytic cells in sputum or bronchial washings appear to be almost invariably associated with malignant neoplasms.

Another group of neoplasms of the lungs which show good exfoliation and can be detected by the examination of sputum or bronchial washings is that of the alveolar cell carcinomas. A cytologic feature which may help in the recognition of this type is the not infrequent presence of multinucleated cells of a rather characteristic appearance.

Of the non-malignant conditions, one which may occasionally display a distinctive cytology is bronchiectasis. Clusters of atypical cells which are sometimes found in this condition show considerable resemblance to clusters of neoplastic cells. The normal structure and the uniformity of their nuclei are a help in interpreting them correctly.

In our laboratory we attribute equal importance to the examination of sputum and to that of bronchial aspirates and washings. We have had instances of positive cases in which the sputum was negative and the bronchial washing positive, but other cases in which the contrary was true. When findings are negative at least three specimens should be examined.

In order to secure a good preservation of the cells we fix the sputum specimens in 70 per cent alcohol as soon as collected. The bronchial washings are mixed immediately with 95 per cent alcohol and then centrifuged. Smears prepared from the sputum, as well as those prepared from the sediment of the bronchial washings, are fixed again in alcohol-ether and stained by our standard smear-staining procedure which insures a good differentiation between basophilic and acidophilic cells. This differentiation is most important for the detection of the acidophilic and orangeophilic cells which are a characteristic feature of the squamous cell carcinomas.

In the urinary tract the most successful application has been in carcinomas of the bladder. As a rule, carcinomas of this organ exfoliate copiously and the cells usually appear in clusters showing structural abnormalities which reveal their malignant nature. In two instances an unsuspected carcinoma, concealed in a diverticulum of the bladder, has been detected by the use of the smear technic.

Papillomas also exfoliate profusely and show great variation in their cytologic picture. Some throw off normal cells, the most characteristic of which are those having a columnar form, others shed abnormal cells with distinct, malignant features, while in an intermediate group the exfoliated cells show an admixture of normal and abnormal types. Cytologic findings may thus be of value in determining the benign or malignant nature of a papilloma. We have repeatedly had cases in which the diagnosis of a malignant papilloma was established by the smear method. In one of these, in which the smear report was positive, a first biopsy was interpreted as negative, and it was only by a second biopsy performed 13 months later that the malignant nature of the tumor was confirmed.

In prostatic carcinomas our progress has been rather slow, due to the fact that for a long time only voided urine specimens were sent to us for examination. The chances of finding prostatic cells in such specimens are rather small. We now require three specimens, one of a prostatic secretion and two of voided urine, one obtained before and one after a prostatic massage. With such specimens the probability of recovering carcinoma cells is greatly enhanced. However, our knowledge of the normal and malignant cytology of the prostate is still incomplete, and there are several cell types, the nature of which can not yet be satisfactorily interpreted.

In some of the prostatic carcinomas the exfoliated cells and their nuclei display very pronounced malignant characteristics. In others the cells are relatively small and of rather uniform structure, making more difficult the recognition of their malignant nature. There is good reason to believe that with increased cytologic knowledge and with the availability of more adequate specimens the smear method in the diagnosis of prostatic neoplasms will reach a much higher level of standardization and accuracy.

Neoplasms of the ureters and of the pelvis of the kidney usually show good exfoliation, as do those of the bladder. In several instances the diagnosis of malignancy has been established chiefly by the cytologic examination of urine sediment. In one case, in which an operation was performed almost exclusively on the strength of repeated positive smear findings, a very early carcinoma of the pelvis was found.

Exfoliated cells deriving from the pelvis of the kidney may be recovered in catheterized bladder, or even in voided, urine, but they appear in much larger numbers in ureteral specimens. Unfortunately such ureteral specimens show marked variability in their cytologic picture, which is apt to lead to misinterpretation. Bi- or multinucleated cells, or cells with greatly enlarged nuclei, are quite frequently encountered. There have been instances in which as many as 60 or 80 nuclei have been noted in a single cell. However, the nuclei of all these atypical cells retain their normal structure and do not show the extreme aberrations which are found in the nuclei of malignant cells.

Carcinomas of the kidney show a considerable variability in their exfoliation. In some instances the exfoliation is so profuse that malignant cells are found in large numbers in a voided urine specimen, whereas in others it is

very scanty. The specific cytology of various types of tumors of the kidney still needs further clarification. Special methods of staining may eventually be found to be necessary for the identification of some of these types.

The administration of estrogens causes marked changes in the epithelium of some of the organs of the urinary tract. As a rule, these changes are reflected in the smears. Both the transitional epithelium of the bladder and the glandular epithelium of the prostate may show cellular and nuclear enlargement and an increased production of glycogen as the result of a prolonged estrogenic therapy. Some of the superficial transitional cells change to a type resembling that of the cornified small-nucleated acidophilic squamous cells found in the vaginal secretion.

It is of interest that a prolonged administration of estrogens in prostatic carcinomas may cause an enlargement not only of the normal but also of the cancer cells, thus greatly facilitating their recognition in the smears. It is, therefore, likely that the use of estrogen therapy prior to the smear examination will tend to increase exfoliation and to cause cytologic changes that would help in the identification of exfoliated cancer cells. Such a use of estrogens has been proved to be of value in carcinomas of the female genital organs.

With regard to the matter of obtaining suitable urine specimens it may be stated in general that catheterized specimens are preferable to voided, more necessarily in women because of the admixture of vaginal cells in voided urine. The types of urine specimens required for the diagnosis of lesions of the prostate or of the ureter and kidney have already been mentioned.

The urine is mixed with an equal amount of 95 per cent alcohol as soon as collected.* It is subsequently centrifuged, and smears prepared from the sediment are fixed again in an alcohol-ether solution and then stained by the same method used for other smears.

Special difficulties are encountered in the use of the smear method for the diagnosis of gastric carcinomas. Of these the two most important are the relatively rapid deterioration of exfoliated cells in the gastric fluid and the continual emptying of the gastric contents into the intestines, which does not allow a sufficiently large accumulation of exfoliated cells within the stomach. Another adverse factor is the rather frequent presence of extraneous cells in the gastric fluid. Clusters of cells from the nasal and bronchial mucosa and dust cells are those apt to be the most troublesome.

Despite these drawbacks the cytologic method is of recognized value in the diagnosis of gastric carcinomas. By improving our cytologic criteria and our technical procedures we hope to bring this application up to much higher standards, although the percentage of false negatives will most likely remain higher in this than in other applications.

* The procedure of fixing specimens immediately and prior to centrifugation by mixing them with equal amounts of 95 per cent alcohol applies to all fluids with the exception of pleural and peritoneal fluids. These are mixed with equal amounts of 50 per cent alcohol, as the 95 per cent alcohol causes a much greater coagulation of proteins, which tends to reduce the amount of sediment.

Fluid aspirated from the duodenum is mostly acellular and, as a rule, it offers very little in the way of positive information. There are, however, cases which demonstrate its occasional value, such as one that we had of carcinoma of the pancreas, in which a positive diagnosis was established by the recovery of cancer cells in the duodenal drainage.[2]

For the gastric application, aspirates as well as washings may be used. Saline washings prove to be the most satisfactory. Gastric specimens should be centrifuged and smears prepared from the sediment without delay in order to insure a good preservation of the cells.

The difficulty in obtaining good specimens from the lower bowel, free from fecal contamination, has been the main reason why the cytologic study of specimens of this type has not, up to now, been given the attention which it actually deserves. Recent technical improvements have put this application on a more practical basis. A cathartic followed by a hot soap enema the next morning generally clears the lower part of the intestine sufficiently to make it possible to obtain a clean saline washing.

Smears prepared from the centrifuged specimens of such rectal washings show good cellular preservation. The relatively uniform cytology of smears of this type greatly facilitates the recognition of malignant cells.

Normal cells from benign rectal polyps can be easily identified by their columnar form. Their nuclear structure remains normal and contrasts with that of the abnormal nuclei found in adenocarcinomas of the rectum. Whenever a lesion is visible, a direct smear is a valuable supplement.

The cytologic technic is also successfully applied to the pleural and peritoneal fluids. The cytology of these fluids is relatively simple, yet we often find it difficult to differentiate accurately between cancer cells and atypical mesothelial cells or histiocytes, which are frequently present in these fluids. In this application a special staining technic permitting a safer identification of the histiocytic elements would be of great value.

Malignant neoplasms of other parts of the body may be diagnosed by the use of the same technic. Carcinomas of the esophagus may be detected through the cytologic examination of esophageal and gastric aspirates and sometimes of sputum. Laryngeal carcinomas can be diagnosed by sputum or by scraping or swab smears. Carcinomas of both the esophagus and the larynx shed copiously. Cells of carcinomas of the gall bladder may be found in fluid aspirated from that organ. Antrum carcinomas may be detected by the examination of washings. Cystic growths may be explored by aspiration. Breast tumors often yield a sufficient amount of secretion to make their diagnosis possible. Tumors of the skin or of the oral cavity may be identified by the examination of scrapings.

Some of these applications have hardly been touched thus far. It will take many years before they have been fully explored and before their comparative cytology has been thoroughly scrutinized. In attempting to evaluate this method we should therefore take into consideration not only its actual status but its future potentialities as well.

As far as actual results are concerned it may be safely stated that certain applications, such as those of the female genital tract and of the respiratory tract, have been advanced to a point where they can now be used in routine laboratory diagnosis. There is an increasing number of publications dealing with the practical advantages and disadvantages of the method and giving an estimate of its dependability as a diagnostic procedure. Although the results obtained by investigators in different laboratories are at variance in some respects, they do permit one to arrive at certain conclusions, in which there is more or less general agreement.

One important point on which there is evidence of such an agreement is that the cytologic method is not to be considered as a method of final diagnosis and that confirmation of smear findings by biopsy or curettage is indicated wherever possible.

On the other hand, it is generally conceded, even by those who are most skeptically inclined, that this method is of unquestionable value in the detection of early or unsuspected carcinomas of certain organs, and is, therefore, particularly adapted to screening purposes. It is also highly useful in evaluating the effects and in following up the results of irradiation or other therapy.

With regard to the diagnostic accuracy of the method, it would be very difficult to make an overall statistical evaluation which would apply to all groups. Figures given out by various investigators show considerable variation. What we are striving for in our laboratory is to limit to a minimum the percentage of false positives. We feel that an accuracy of over 95 per cent can and should be maintained in the cases reported as Class IV and of over 98 per cent in those reported as Class V.* Anything below these figures would not be at all satisfactory, more particularly in the Class V group, in which reports are often used as the basis of a decision for a major operation. Negative reports, as a rule, show a higher percentage of errors, ranging from 5 or 10 per cent, in well explored gynecological cases, to 25 per cent or even more in other applications, more specifically in the gastric.

Some of the drawbacks of the cytologic method are that it is time consuming and that it requires special study even on the part of men with a good pathological background. These disadvantages constitute a serious obstacle to the incorporation of the method in many laboratories and will, no doubt, greatly retard its more widespread adoption. What is more discouraging is the fact that in some laboratories, because of an increasing demand, the method is introduced prematurely, and is put into practice by men who have

* Classification of reports on smears as applied to the diagnosis of malignant neoplasms

Class		
I	Negative	Absence of atypical or abnormal cells
II	Negative	Atypical cells present but without abnormal features
III	Suspicious	Cells with abnormal features suggestive of but not conclusive for malignancy
IV	Positive	Cells and cell clusters fairly conclusive for malignancy
V	Positive	Cells and cell clusters conclusive for malignancy

not had sufficient training. This does considerable harm and tends to discredit the method.

Should one attempt to evaluate the cytologic method and its general significance, he should bear in mind that it is still going through a period of evolution, and that our present achievements do not actually represent our maximum expectations in this new field. There is no doubt that the method possesses great potentialities, not only with regard to its practical usefulness in cancer diagnosis, but also in its more fundamental value as a new branch of the morphological sciences. Judging from the progress that has been made during the last few years we can look forward with confidence to higher future accomplishments. However, many more years of arduous work lie ahead of us if we are to explore this wide new field and to derive all the benefits which might be expected from it.

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CASE REPORTS

ELECTROCARDIOGRAPHIC CHANGES IN A CASE OF WERNICKE'S SYNDROME *

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Eugene Clark, M.D., *New York, N. Y.*

It is well known that the heart may be involved and that electrocardiographic changes are found in conditions due to deficiency of the vitamin B complex. This has been shown to occur in beriberi and pellagra.[1, 2, 3, 4, 5, 6, 7, 8] The following case is of interest because of the occult cardiac involvement with striking electrocardiographic abnormalities, which disappeared rapidly after thiamine chloride therapy, in a patient with Wernicke's syndrome (hemorrhagic polioencephalitis superior), a state which clinical and experimental evidence holds ascribable to thiamine deficiency.[9, 10, 11, 12]

Case Report

A 40 year old white man entered the hospital in a confused state. He was disoriented as to time and place, confabulated, and frequently contradictory. The only history which appeared to be reliable was the admission of chronic alcoholism for at least six years, accompanied by a grossly inadequate food intake. Diplopia of 24 hours' duration was admitted to be present; headache was denied. A questionable history of peptic ulcer was given. No history of heart disease was obtained.

At the time of admission the following physical findings were present: Temperature 99.2° F., pulse 150, respirations 20, blood pressure 114 mm. Hg systolic and 80 mm. diastolic.

The head showed no evidence of injury. The pupils reacted to light and accommodation, and were round, regular and equal. There was left external rectus palsy with diplopia; horizontal, but no vertical nystagmus. The fundi were normal. The ears, nose, mouth, throat and neck were essentially normal.

The lungs were clear to auscultation and percussion. The heart was not enlarged. The sounds were of good quality and regular. Sinus tachycardia was present. There were no murmurs or thrills.

The abdomen was flat and slightly tender in the right upper quadrant. The kidney, spleen and liver were not palpable. Genitalia were normal. The extremities revealed slight cyanosis of both feet and hands.

Neurological examination: Deep tendon reflexes were normal in the upper extremities, absent in the lower extremities. The Babinski reaction was equivocal, and plantar hyperesthesia was present.

Laboratory findings: White blood count 4850; neutrophiles 60 per cent, lymphocytes 33 per cent, mononuclears 2 per cent, eosinophiles 2 per cent, basophiles 3 per cent. Red blood count 4,870,000; hemoglobin 14.5 gm. The Wassermann reaction was negative. Sodium: 312 mg./100 c.c. Non-protein nitrogen: 32 mg./100 c.c.

* Received for publication November 15, 1946.
From the Third (New York University) Medical Division of Bellevue Hospital, and the Department of Medicine of the New York University College of Medicine.

Fasting blood sugar: 87 mg./100 c.c. Erythrocytic sedimentation rate: 26 mm. corrected (normal 0–10). Blood culture: negative. Urine: no abnormalities.

On admission, the diagnosis of Wernicke's syndrome was made. The patient was given 50 mg. of thiamine chloride intramuscularly at 11:00 a.m., and 50 mg. intravenously at 2:00 p.m. The strabismus and diplopia were gone at 4:00 p.m. Thereafter, 50 mg. of thiamine chloride were given daily.

The chest roentgenogram taken on admission was suggestive of tuberculosis. This was confirmed by the finding of acid-fast bacilli in the sputum. Repeated chest roentgenograms were reported as showing a mottled infiltration of the right apex of the lung with a small cavity above the first rib, together with an area of round infiltration 1.5 cm. in diameter in the second left intercostal space. Except for a fever which fluctuated between 100° F. and 103° F. for four days following admission the patient has been afebrile.

The electrocardiograms illustrated were taken on the day of entry, the following day, six days following admission, and 20 days following admission.

The abnormal ST–T complexes in Leads II and III which were seen on the first two days are shown to have reverted to normal by the sixth day.

Subsequent laboratory work performed two weeks following admission revealed: icteric index 5; total protein 8.2; albumin 4.74; globulin 3.46; cholesterol 153.6; cholesterol esters 129.9. The repeated neurological examination revealed the following: a persistence of the nystagmus, slight tenderness in the calf muscles, plantar hyperesthesia, and absent deep tendon reflexes in the lower extremities, normal plantar reflexes. At that time, a moderate adiadokokinesis was noted in the right arm; the muscle strength throughout was normal. The patient walked with a wide gait and lost his balance making quick turns to either side.

The final diagnosis was Wernicke's syndrome and pulmonary tuberculosis.

Discussion

The case herein reported is identified as that of Wernicke's syndrome (hemorrhagic polioencephalitis superior) by the presence of all of the essential features of the disease. The combination of an ophthalmoplegia promptly subsiding after thiamine therapy, with clouding of consciousness, ataxia, other signs of vitamin deficiency (i.e., peripheral polyneuritis), and a dietary history of inadequate thiamine intake, serves to establish the diagnosis.

Though there is nothing specific about the pattern of the electrocardiographic abnormalities which this patient showed, that they were an integral feature of his vitamin deficiency state is indicated by the absence of any clinical evidence of a structural cardiac lesion, by their similarity to electrocardiographic abnormalities previously reported in some cases of beriberi and pellagra,[1, 2, 5] and by the restitution of the electrocardiogram to normal within six days after thiamine therapy was begun. The electrocardiographic abnormalities cannot be ascribed to tachycardia since the ventricular rate 20 days following admission was approximately the same as that on the second day after admission although the electrocardiogram had long since become normal. No digitalis was given.

This case report is of special interest because the patient presented the clinical syndrome of Wernicke which has been ascribed to thiamine deficiency and at the same time presented occult cardiac involvement with marked electrocardiographic abnormalities. This case calls further attention to cardiac involvement associated with vitamin deficiency states and its apparent reversibility following adequate therapy. Routine electrocardiograms in these conditions may reveal

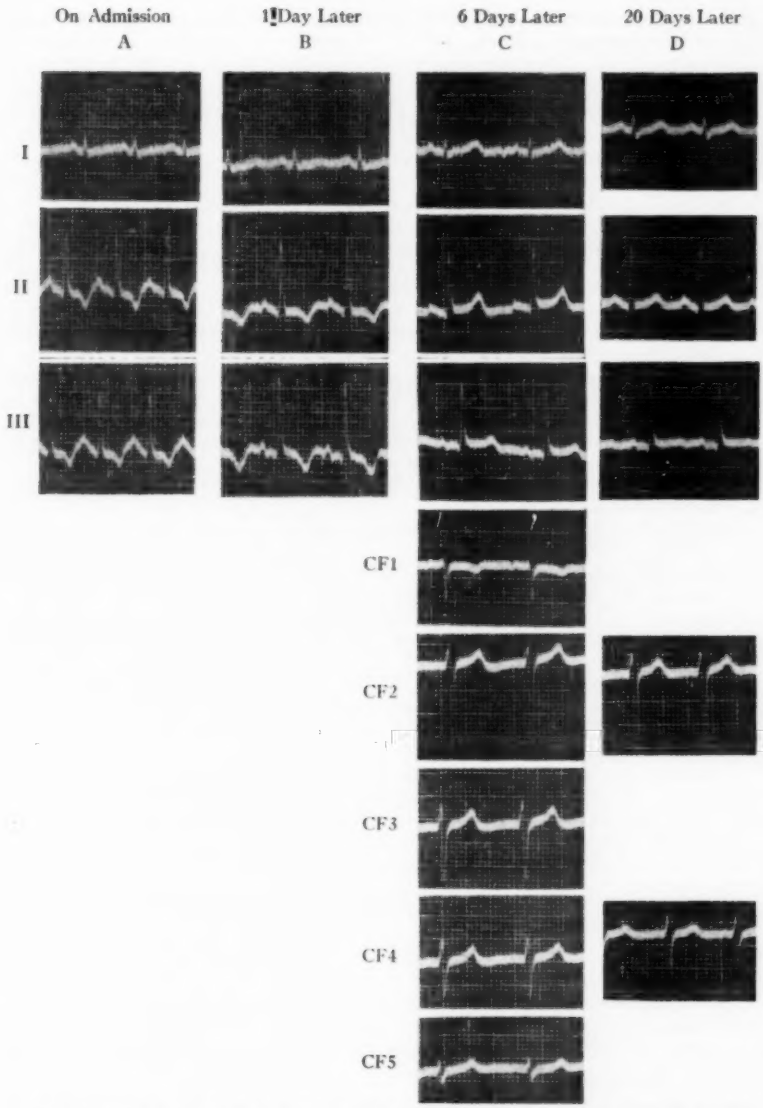

FIG. 1. *A*. On day of admission. Sinus tachycardia of 140. The abnormalities are the low T in Lead I and the inverted T in Leads II and III. *B*. One day later. Sinus tachycardia of 107. The low T in Lead I and the inverted T in Leads II and III persist. *C*. Six days later. Sinus rhythm of 83. The abnormal T waves are now normal as is the entire record. *D*. Twenty days later. Sinus tachycardia of 107. Normal record. The timer was not working while the first three leads were taken.

cardiac involvement before clinical manifestations are present and thereby be of value to the clinician.

Conclusion

A case of Wernicke's syndrome is presented in which occult cardiac involvement with striking electrocardiographic abnormalities was found. Following intensive thiamine chloride therapy, these abnormalities were no longer present.

We are indebted to Dr. L. N. Katz for reading this paper and making suggestions.

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AUREOMYCIN IN ACUTE INFECTIOUS MONONUCLEOSIS *

By B. J. Gruskin, *New York, N. Y.*

Since the discovery of aureomycin,[1] an antibiotic obtained from a mold of the Streptomyces group, *Streptomyces aureofaciens*, investigation has shown it to be extremely effective both in vitro and in vivo against rickettsial organisms of several varieties as well as against certain viruses [2] and bacteria.[3, 4] Several reports have appeared during recent months indicating a singularly striking effectiveness against lymphogranuloma venereum,[5] brucellosis,[6] primary atypical pneumonia [7] and various types of ocular infections.[8] No report, to my knowl-

* Received for publication March 28, 1949.

edge, has as yet appeared in the literature concerning its use in acute infectious mononucleosis. Because of the highly favorable results obtained with it in some viral diseases, it was deemed advisable to try aureomycin * in a pateint with this disease.

Case Report

A white female, age 17, became ill on December 29, 1948 wth malaise and slight fever. On the following day, she developed a sore throat and when she was first seen at her home on December 31, her temperature was 102° F. Examination at that time revealed the presence of a yellowish-white exudate on both faucial tonsillar stubs as well as on discrete lymphoid tissue deposits on each postero-lateral pharyngeal wall. The exudate assumed a follicular distribution. On either side of the neck, below the angle of the mandible, a solitary lymph node was enlarged and tender but no other lymph glands were palpable. She was given 300,000 units of penicillin in oil intramuscularly that day and on each of the next five days, a total of 1,800,000 units, without any beneficial effect on the course of the illness. Her temperature continued, fluctuating between 100.5° F. and 102° F. until January 4, 1949 and between 102° F. and 104.5° F. until January 7. The exudate, originally in a follicular pattern, now assumed a membranous appearance, involving not only the original sites, but the base of the tongue and the hypopharynx as well. The nasopharynx could not be seen but the clinical condition suggested involvement there, too. She developed a moderate cough with pain in the upper retro-sternal region. On January 5, the eighth day of the disease, the spleen was palpable. The submaxillary glands originally involved remained unchanged but a posterior cervical gland on either side became enlarged and tender. The patient was obviously quite toxic.

A blood count on the seventh day of illness revealed: hemoglobin, 16.7 gm. (104 per cent); red blood cells, 5,100,000; white blood cells, 9200 with a differential count of 33 per cent polymorphonuclear neutrophiles, 65 per cent small lymphocytes and 2 per cent monocytes. The serum of blood taken the same day for heterophile antibody determination gave a positive agglutination in a dilution of 1:1792. Two throat cultures during the first six days were sterile for the diphtheria bacillus, positive for *Staphylococcus aureus* and gram negative diplococci.

Aureomycin was started orally at 1 p.m. on the tenth day of the disease on the morning of which the temperature reached 104.5° F. One hour before therapy was begun, however, the temperature dropped to 102° F. After 2.75 gm. were administered during the first 24 hours, the temperature dropped to 98.8° F. (figure 1). She received 2 gm. during the next 24 hours, her temperature varying between 98.8° F. and 100.5° F. After having had 3.75 gm. she developed some nausea and, on one occasion, vomited. The nausea, of slight degree, persisted for about 36 hours when she had two loose bowel movements. The dose for the third day, therefore, was reduced to 1.5 gm., a similar dose being given on the fourth day. The temperature assumed a normal level on the third day, there being no subsequent rise. A final dose of 1 gm. was given on the fifth day, making a total of 8.75 gm.

Twenty-four hours after treatment was begun, the patient no longer appeared toxic although she still had considerable dysphagia; the cough and retro-sternal distress disappeared; the spleen was no longer palpable; the enlargement and tenderness of the cervical glands were unequivocally less, reaching a normal state 96 hours after therapy was started. No other glands became palpable. There was no change in the pharyngeal exudate until 48 hours after the drug was begun, at which time several of the lesions began to shrink at their periphery and the dysphagia was minimal. Three days later, the throat was entirely clear.

* Aureomycin was obtained through the courtesy of Lederle Laboratories Division, American Cyanamid Company.

A blood count done 24 hours after inception of treatment indicated a white cell count of 7800 with 35 per cent polymorphonuclear cells, 58 per cent small lymphocytes, 5 per cent large lymphocytes and 2 per cent eosinophiles. One done at the termination of treatment revealed 6200 white cells with 42 per cent polymorphonuclears, 51 per cent small lymphocytes, 1 per cent large lymphocytes, 4 per cent eosinophiles and 2 per cent monocytes. The heterophile antibody determination on the twenty-first day of the disease, 11 days after treatment was begun, showed a positive agglutination in a dilution of 1:896. On the next day, a blood count revealed the following: hemoglobin, 13.5 gm. (84 per cent); red blood cells, 4,200,000; white blood cells, 5,900 with 35 per cent polymorphonuclears, 51 per cent small lymphocytes, 3 per cent large

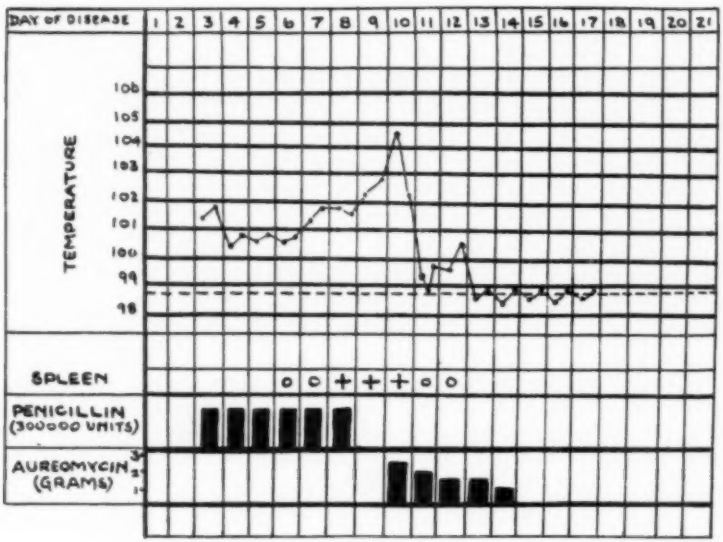

FIG. 1.

lymphocytes, 10 per cent eosinophiles and 1 per cent monocytes. The lymphocytes in all blood smears were abnormal to a large degree.

COMMENT

Infectious mononucleosis is, of course, a self-limited disease, lasting a few weeks to a few months, and it is extremely difficult to appraise any therapeutic agent in a disease of this type. McKinley and Downey,[9] analyzing a large group of cases, state that the temperature, after a daily increase during the first week, tends to subside, followed occasionally by one or two wave-like recrudescences before it becomes normal after a total duration varying up to 26 days. The average duration of illness of 45 cases was 14.4 days. However, they mention also that all the cases with prolonged course were those with some type of respiratory infection and with a marked degree of tonsillar and pharyngeal exudate. The

case reported here might well fit into that category and it may well be that the normal course of this patient's illness would have been prolonged. In this case, it is noteworthy that, coincident with the use of aureomycin, the following changes in the clinical course of the disease occurred within 24 hours:

1. A significant drop in temperature.
2. The spleen was no longer palpable.
3. The patient became markedly less toxic.
4. There was definite diminution in the swelling and tenderness of the cervical lymph nodes.

These observations warrant further clinical trial of aureomycin in infectious mononucleosis.

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HYPERTROPHIC OSTEOARTHROPATHY; REPORT OF A CASE ASSOCIATED WITH A CHORDOMA OF THE BASE OF THE SKULL AND LYMPHANGITIC PULMONARY METASTASES *

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Much knowledge regarding the clinical aspects of hypertrophic osteoarthropathy has been acquired in the past half century. Its etiology and mechanism, however, remain to be elucidated. In the majority of cases, osteoarthropathy, with its concomitant clubbing of the fingers and toes, is seen as a sequel of chronic suppurative or neoplastic disease of the thoracic organs, less commonly

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of the abdominal viscera. Only in rare instances has the condition been known to precede the manifestation of the underlying disease. When this occurs, diagnosis is often impossible until late. The following is an illustrative case.

Case Report

J. S., a 21 year old white prisoner of war, first became ill early in January 1944. The only significant illness in his past history was rickets during childhood which left him with slight bowing of the legs and moderate curvature of the spine. Up to the time of the present illness, he had felt entirely well and was able to perform hard manual labor. His weight in December 1943 was 168 pounds. Early in January 1944 he first began to complain of temporal and frontal headaches which were unrelieved by symptomatic treatment. Shortly afterward there developed lower abdominal pain associated with constipation and anorexia, and later, nausea and vomiting. Within a month there followed pain in the right side of the neck with torticollis and diminished hearing in the right ear. Upon admission to an Army Station Hospital on April 6, 1944, he had lost 25 pounds in weight and felt very weak. Physical examination at this time was recorded as negative save for slight fever, weakness and weight loss. Laboratory examinations of blood, urine, spinal fluid and basal metabolism were also negative except for slight anemia (hemoglobin 12 grams, red blood count 4 million), and elevated sedimentation rate (40 mm. per hour). Cholecystography, barium enema, and intravenous pyelography failed to disclose abnormalities.

The abdominal symptoms gradually subsided and the headaches became less severe. However, moderate fever up to 101° F., progressive weakness, and loss of weight continued. Aching pains in the limbs developed soon after admission, and clubbing of the fingers and toes became apparent. Roentgenograms revealed periosteal proliferation of the metacarpals and metatarsals, as well as of the bones of the forearms and legs. Roentgenographic examination of the spine was negative except for dorsolumbar scoliosis, and that of the skull revealed some irregularities in the region of the sella turcica which had the appearance of new bone production. A chest roentgenogram on April 26 was reported as normal. Early in May the patient began to complain of pain in the right lower chest aggravated by breathing. This symptom, at first intermittent, gradually became more severe and persistent with little relief until death. There was no cough nor expectoration. Fluoroscopy following the onset of chest pain revealed no cardiac nor pulmonary abnormality. However, a roentgenogram taken five weeks later disclosed infiltrative lesions of the right hilar and costophrenic areas (figure 2, c). The patient was transferred to a General Hospital for further investigation on June 15, 1944.

On physical examination at the time of admission, the patient appeared chronically ill and cachectic. The skin was dry and in many areas ichthyotic. The head could be rotated only with difficulty because of pain in the neck. There was exquisite tenderness of the right sternocleidomastoid muscle. Hearing in the right ear was markedly diminished. Moderate trismus was present. The pharynx could be seen sufficiently and was found normal. Except for tachycardia, the heart was normal. Blood pressure was 118 mm. Hg systolic and 75 mm. Hg diastolic. Examination of the lungs revealed impaired resonance with diminished breath sounds and showers of fine crepitant râles over the right lower lobe. Examination of the abdomen was negative. The fingers and toes were considerably clubbed with marked parrot-beak deformity of the nails. The forearms and legs were enlarged and thickened, giving the limbs a hypertrophic appearance in spite of the considerable atrophy of the musculature of the thighs and arms (figure 1, a and b). The patient experienced intense pain even on slight pressure over the long bones. Muscular weakness was marked in all the extremities. The cervical, axillary and other regional lymph nodes were not palpably enlarged. Rectal examination was negative. The prostate was normal to palpation.

but the testicles were much smaller than usual. Studies of ocular fundi disclosed slight papilledema with tortuosity of the veins, more marked on the left. These changes became more pronounced on subsequent examinations. Neurological examination one week after admission revealed exaggerated patellar and Achilles tendon reflexes, the sign of Babinski on the right and a questionable response on the left. Position sense was absent on the right and impaired on the left. Diplopia was noted when the object was at the extreme left; this became progressively more marked within the next two weeks. Bronchoscopy was attempted, but could not be performed because of trismus.

FIG. 1. *a* and *b*: Appearance of patient three weeks before death. Note thickening of forearms and legs.

The subsequent course in the hospital was dominated by increasing clinical and roentgenographic signs of pulmonary involvement. The patient developed cough with moderate expectoration. Rapidly increasing signs of infiltration of the right lung and pleural effusion were followed by similar involvement on the left. The periosteal changes became extremely marked (figure 2, a and b) and extended to the distal ends of the femora and humeri. Atrophy occurred about the joints. Roentgenograms of the skull revealed marked osteoporosis of the sella turcica with some erosion of the floor and the posterior clinoid processes (figure 2, d). The sedimentation rate was persistently elevated: up to 52 mm. per hour. The blood calcium was 11.7 mg. per cent, phosphorus 4.2 mg. per cent, alkaline phosphatase 5.9 Bodansky units; white blood count and differential were within normal limits; red blood count was between 4.0 and 3.6 million, with hemoglobin between 12 and 10.8 grams per cent. During the last few days before death fever increased, with irregular elevations up to 103° F. Progressive embarrassment of respiration with cyanosis occurred and was followed by coma and death on July 14, 1944, approximately six months after the onset of symptoms.

Autopsy. The autopsy was performed eight hours after death. Only pertinent findings are recorded.

Gross Examination. Skull: The bones of the skull cut with usual resistance. The meninges were smooth, the subarachnoid fluid clear and colorless and not increased in amount. The vessels of the brain were markedly injected. The base of the

skull in the region of the sella turcica was elevated in an irregular fashion. The bone in this area was almost completely replaced by a firm grayish mass, uniform in appearance and consistency, except for occasional small grayish mucinous areas and embedded spicules of the original bone (figure 3, b). The mass extended to the pharyngeal vault, producing an ulceration about 2 cm. in diameter, and spreading under the mucosa along the posterior wall of the pharynx, into the nasal choanae and septum. On the cerebral side the mass elevated the entire sella turcica, destroying its floor and

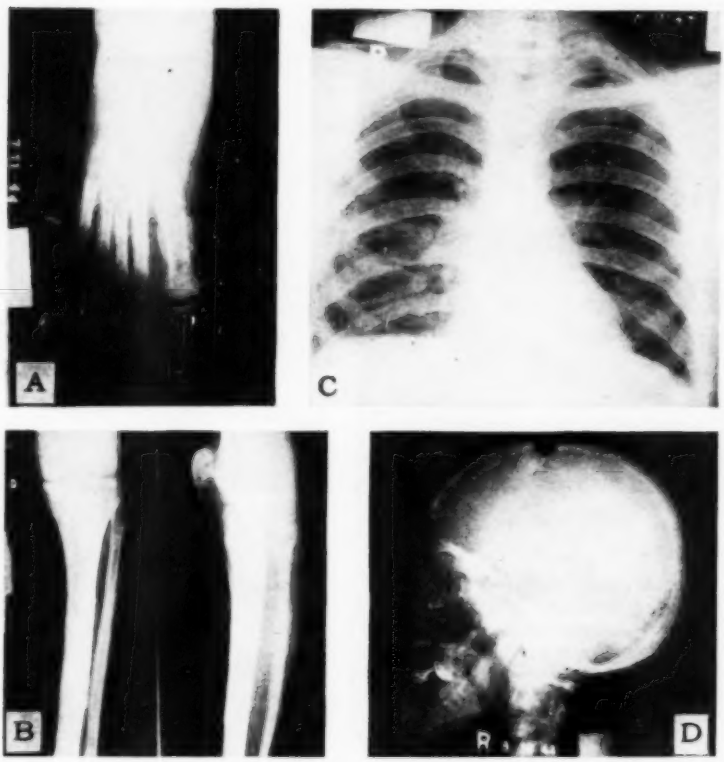

FIG. 2. *a* and *b:* Periosteal proliferation of the metatarsals and bones of the legs. *c:* Earliest pulmonary changes shown by roentgen-ray; involvement of the right hilus. *d:* Roentgenogram of the skull four weeks before death. Osteoporosis of the sella turcica.

compressing and apparently invading the pituitary. It also raised the anterior part of the Clivus Blumenbachii and appeared to press upon the pons. However, at no point did it perforate the dura. Anteriorly, it spread into the sphenoid sinuses, and laterally into the cavernous sinuses, surrounding the carotid arteries. On the left the mass produced a dome-shaped elevation near the tip of the temporal pyramid and extended in the direction of foramen lacerum.

Examination of the brain after fixation revealed no significant abnormalities except for slight flattening of the pons.

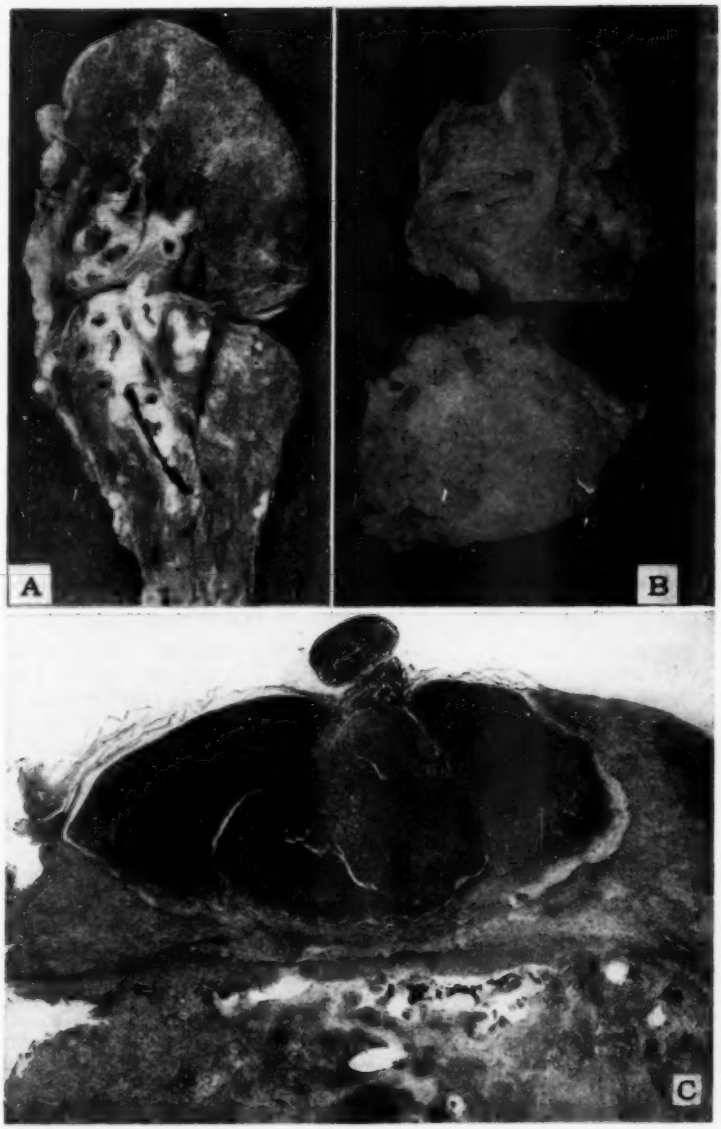

FIG. 3. *a:* Section of the right lung showing peribronchial and perivascular spread of the tumor. *b:* Tumor at the base of the skull and roof of the nasopharynx. *c:* Relation of the tumor to the pituitary gland. Note complete destruction of the sella turcica and the few remaining bony trabeculae within the tumor (× 10).

Chest: The right pleural space contained 1100 c.c. and the left, 300 c.c. of slightly bloody fluid. The lungs were bound to the walls of the chest by fibrous and fibrinous adhesions. The parietal and the visceral pleurae were covered by large confluent plaques composed of firm grayish-white tissue, varying in thickness from a few millimeters to a few centimeters. The lungs weighed 500 grams each; the left lung had three lobes. The parenchyma of both lungs was uneven in consistency, being firm in the hilar regions and softer although nodular towards the periphery. On section, the hilar structures were encased in dense firm grayish-white tissue which formed an almost continuous mass (figure 3, a). It followed the finer subdivisions of bronchi and vessels, forming a mantle of varying thickness. The right lower lobe was most extensively involved, but no part of the lungs was spared. In many places the tumor tissue had compressed and invaded the bronchial walls; however, there were no apparent breaks in the mucosa, and no complete obstruction of any of the lumina.

The lymph nodes of the posterior mediastinum, including the peribronchial, peritracheal and para-aortic, were large and firm. On section the normal markings were obliterated by dense grayish-white tissue. The abdominal para-aortic nodes above the level of the renal arteries showed similar changes. Other lymph nodes of the body were not abnormal.

The heart and the organs of the abdominal cavity showed no significant gross changes. The testes were small, weighing 10 grams each; the cut surface did not string well.

Extremities: The distal parts of all four extremities were thickened and enlarged. The hands and feet were covered with wrinkled skin. The terminal phalanges of fingers and toes were considerably thickened. There was cyanosis of the nail beds. The proximal half of the right fibula was removed. Its surface was markedly irregular and almost completely covered by thickened periosteum and newly formed cancellous bone (figure 5, a). On cross section, the original compact bone appeared unchanged. The marrow cavity was narrow and contained a small amount of reddish-yellow marrow.

Microscopic Examination. Tumor in the base of the skull: The bulk of the tumor below the sella turcica was composed of elongated or stellate cells forming a fairly loose syncytial meshwork (figure 4, a and b). The cells had quite abundant eosinophilic cytoplasm and large nuclei often containing distinct nucleoli. Many cells possessed large vacuoles in the cytoplasm giving them a "signet ring" appearance. The intercellular spaces were filled with pale, clear, faintly fibrillar substance suggestive of mucus. Here and there were occasional strands of connective tissue and small blood vessels, as well as small eroded spicules of bone. A few areas of necrosis were seen.

Towards the roof of the nasopharynx the tumor became more cellular (figure 4, c). The cells were smaller, more cuboidal in shape, with less cytoplasm and darker nuclei. They were often arranged in a single row around small irregular spaces and were surrounded by dense eosinophilic ground substance, reminiscent of connective tissue. There were fewer vacuolated cells and little intercellular mucus. In some places the cells markedly predominated over the ground substance; in other places they were widely scattered. In some areas clusters of loosely packed cells were found in the lymphatics. Blood vessels were not numerous. The tumor diffusely infiltrated the pharyngeal muscles and the mucosa, destroying the normal architecture; however, intact mucosa, glands and lymphoid tissue could be seen in many places. The ulceration was covered with necrotic tumor tissue and polymorphonuclear leukocytic exudate.

Sella turcica and pituitary: The tumor had completely destroyed the bony confines of the pituitary gland (figure 3, c). It also filled the cavernous sinuses, surrounding the carotid arteries. The pituitary gland was invaded in one area by tumor tissue similar in structure to that seen in the roof of the nasopharynx. The cells of

the gland were well preserved, the majority having distinctly eosinophilic cytoplasm. Along the periphery of the gland were several small areas of necrosis.

Lungs: Sections from various parts of the lungs showed a similar microscopic picture. The perivascular, peribronchial and subpleural lymphatics were markedly

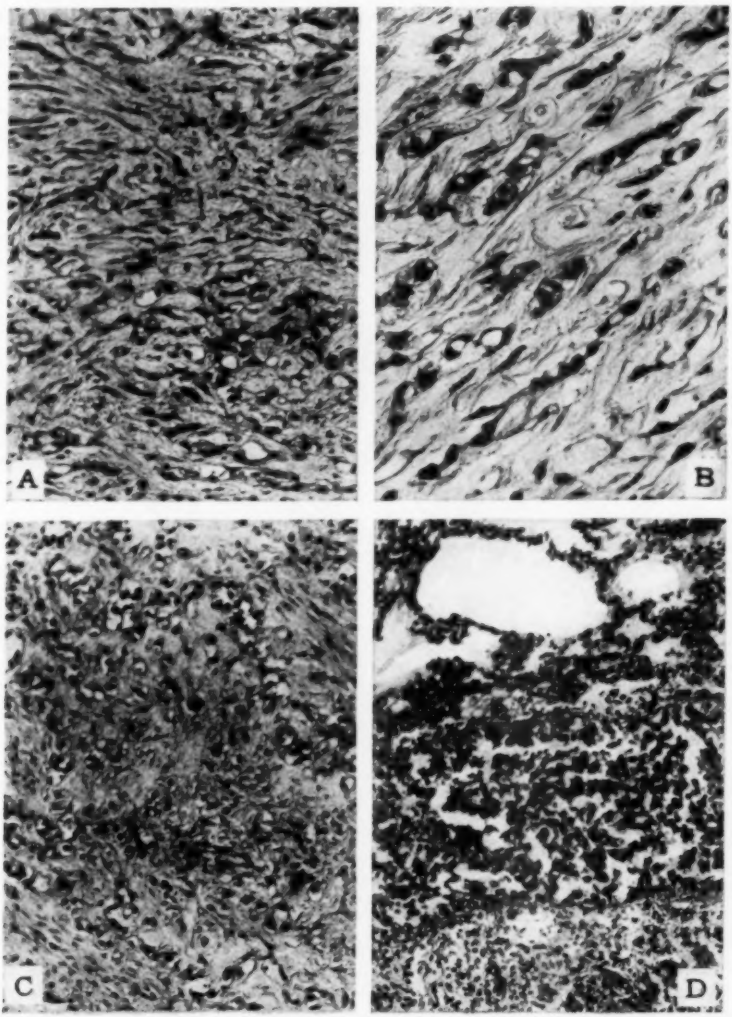

FIG. 4. *a* and *b:* Tumor at the base of the skull showing syncytial meshwork of elongated and stellate cells, "signet ring" cells and the faintly fibrillar, transparent intercellular substance ($A - \times 180$; $B - \times 350$). *c:* Tumor invading the roof of the nasopharynx. Variation in appearance of cells ($\times 180$). *d:* Tumor cells in a pulmonary lymphatic ($\times 160$).

distended with masses of tumor cells very similar to those found in the lymphatics of the nasopharynx (figure 4, d). The cells were polygonal but with poorly defined limits, giving the impression of a continuous though fairly loose syncytium. The cytoplasm was distinctly eosinophilic, and the nuclei, large and oval or polygonal. Only very few vacuolated cells were seen and there was no intercellular mucus. A considerable amount of necrosis was found in the larger nodules, with polymorphonu-

FIG. 5. *a:* Gross appearance of the right fibula. *b:* Cross section of fibula, showing thick periosteum and newly formed bone (×6).

clear leukocytes intermixed with the tumor cells. In some areas the neoplasm appeared to break out of the lymphatics and infiltrate the adjoining parenchyma and the walls of the smaller blood vessels and bronchi. At one point, in the right main bronchus, the tumor had actually reached the lumen. The parenchyma especially in the right lower lobe was compressed and atelectatic; many alveoli contained edema fluid and polymorphonuclear leukocytes; others were filled with tumor cells. Occasional small blood vessels were occluded by fibrin thrombi.

Pleura: The pleura was markedly thickened by masses of tumor tissue, reproducing the structure of the tumor in the base of the skull. Small areas of elongated cells mixed with considerable mucinous intercellular substance, alternated in an irregular fashion with large areas of dense ground substance containing nests of cuboidal cells arranged about small empty spaces. There was a fair number of "signet ring" cells and also many elongated cells resembling fibroblasts. Areas of necrosis were fairly numerous.

Para-aortic lymph node: The lymphoid tissue was almost completely replaced by the tumor exhibiting the same pattern as in the pleural metastases. Some of the sinusoids and many of the lymphatics in the immediate vicinity were filled by syncytial masses of cells as seen in the pulmonary lymphatics.

Testis: Tubules were well developed but showed incomplete spermatogenesis.

Fibula: The original structure of the bone was well preserved, though widening of many of the Haversian canals suggested resorption. The marrow cavity was filled with fat. Superimposed upon the original cortex was a thick irregular meshwork of newly formed trabeculae, covered by thickened periosteum (figure 5, b). The intertrabecular spaces were filled with loose connective or fatty tissue containing occasional clumps of small round cells.

Comment

The autopsy confirmed the clinical impression of extensive neoplastic involvement of the lungs, and massive hypertrophic osteoarthropathy. The changes at the base of the skull were caused by a malignant tumor identical in structure with that found in the chest. The involvement of the lungs was of "lymphangitic" variety with only secondary infiltration of the parenchyma, bronchial walls and blood vessels. There was no particular area which could have been designated as the primary focus. This fact argued against primary pulmonary neoplasm with metastases to the base of the skull. Reconsideration of the clinical course and detailed histological studies led us to believe that the converse, in fact, was true, that the tumor originated within the base of the skull and metastasized to the lungs and pleura.

The microscopic structure was characterized by the presence of fairly large elongated and polygonal cells with varying amounts of eosinophilic cytoplasm, often containing large vacuoles, and by abundance, in some areas, of clear intercellular mucinous substance. Though the typical "physaliferous" cells are missing, the polymorphous appearance with syncytial-like structure, vacuolization of the cytoplasm, accumulation of intercellular mucinous substance and tendency to arrangement around clear spaces, strongly suggest the diagnosis of chordoma. The topography of the tumor, the location of the most differentiated areas beneath the sella turcica, and the expansion of the involved bones testifies to the intraosseous origin of the growth. These features also help to exclude other tumors at the base of the skull, such as lympho-epithelioma and transitional cell carcinoma of the nasopharynx or sphenoid sinuses. The subsellar, intrasphenoid

craniopharyngioma might present similar gross features, but histologically it is usually a variant of squamous cell carcinoma.

Metastasizing chordomas of the base of the skull are not at all uncommon. Faust et al.[1] quote Mabrey's tabulation of 10 such instances among 27 autopsied cases of spheno-occipital chordoma, with involvement of lymph nodes, lungs, liver and other organs. However, even the malignant chordomas have a relatively slow course and may extend over a period of years. Cases such as presented here, with rapid course and massive "lymphangitic" metastases, must be very rare. Bruce and Mekie [2] postulated that tumors resembling the early stages of notochordal development with non-vacuolated polygonal cells are most malignant, while those resembling the later stages when cells become vacuolated and produce intercellular mucinous substance, are least malignant. In our case, vacuolated cells were in the minority, and intercellular substance was seen only in the central parts of the tumor, while the periphery, invading the pituitary and the nasopharynx, was characterized by non-vacuolated polygonal cells. Tumor thrombi in the lymphatics of the nasopharynx and the lungs contained cells almost exclusively of the latter type, whereas at the sites of secondary implantation, in the lymph nodes and the pleura, differentiation and production of mucus took place.

To reconstruct the pathogenesis of the disease, an expanding lesion in the skull first manifested itself in uncontrollable headaches. The headaches subsided spontaneously, perhaps at the time when the tumor broke through into the nasopharynx, thus relieving the tension. It is reasonable to assume that nausea, vomiting and other intestinal symptoms were also an expression of pressure on the brain stem and that their relief can be explained by the same mechanism. The subsequent neurological manifestations were caused not so much by increased intracranial pressure, as by direct pressure upon the brain stem. Infiltration of the nasopharynx accounts for trismus caused by reflex contraction of the internal pterygoid muscle, unilateral impairment of hearing, probably due to edema of the Eustachian tube, and torticollis, a manifestation of eleventh nerve involvement. The tumor invaded nasopharyngeal lymphatics, and, bypassing the cervical lymph nodes, metastasized to the chest. The pulmonary involvement produced no chest symptoms for a considerable length of time, during which it was confined to the lymphatics, yet it was accompanied by rapid and extensive hypertrophic osteoarthropathy. The changes in the long bones were typical of the latter condition. They consisted of marked deposition of newly formed bony trabeculae under the periosteum and thickening of the periosteum itself. The joints were not examined at autopsy, but roentgenograms demonstrated atrophic changes about the knees and ankles.

Various theories have been propounded to explain the mechanism of hypertrophic osteoarthropathy and clubbing of fingers. These have been discussed in a comprehensive and analytical review by Mendlowitz.[3] Many of the theories, such as trophic, nervous, infectious, etc., have only historical interest. Local circulatory disturbances have received considerable attention, with some authors ascribing the changes to capillary stasis, and others to increased blood flow.[3] Marie [4] and also Bamberger,[5] who were the first to describe hypertrophic osteoarthropathy, believed it to be caused by toxins emanating from the suppurative foci within the chest. However, the condition may follow neoplastic disease without infection. It is apparent that none of the theories thus far suggested can adequately explain all instances. Recently Fried,[6] in reporting four cases

of pulmonary neoplasm with hypertrophic osteoarthropathy, emphasized the similarity of certain aspects of this condition to acromegaly, and suggested dyspituitarism as a probable cause. This hypothesis was supported in his cases by acromegalic features, atrophy of testes and gynecomastia in the male, hirsutism and secondary male characteristics in the female, and also by hyperplasia of eosinophilic elements in the pituitary gland. In our case, except possibly for testicular atrophy, no evidence of endocrine dysfunction was observed, yet the pituitary gland showed distinct increase of eosinophilic cells in areas not involved by the tumor. More clinical observations and pathological data are required to establish the rôle of the endocrine apparatus and particularly the pituitary gland in hypertrophic osteoarthropathy. Until then, this theory must be considered an interesting but unproved possibility.

SUMMARY

1. A case of chordoma at the base of the skull is reported.

2. It is characterized by a high degree of malignancy, unusual for chordoma, by lymphangitic pulmonary metastases, and by early and massive hypertrophic osteoarthropathy.

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A CASE OF A PUTRID EMPYEMA WITH A BRONCHO-PLEURAL FISTULA SUCCESSFULLY TREATED WITH PENICILLIN *

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RAPID advances have been made in the treatment of empyema thoracis with the advent of penicillin, especially with its use intrapleurally. In all probability,

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From Veterans Administration Hospital, Minneapolis, Minnesota, and the Department of Medicine, University of Minnesota.
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the full therapeutic potentialities of penicillin have not been fully explored. The classical indications for surgical intervention in the treatment of empyema have been modified extensively by penicillin. Finland et al.[1] expressed the opinion that more than one-half of all cases of empyema can be cured by repeated aspirations and local instillations of penicillin into the pleural cavity.

There is general agreement that certain indications for early surgical treatment persist. Included among these indications are: the presence of a putrid

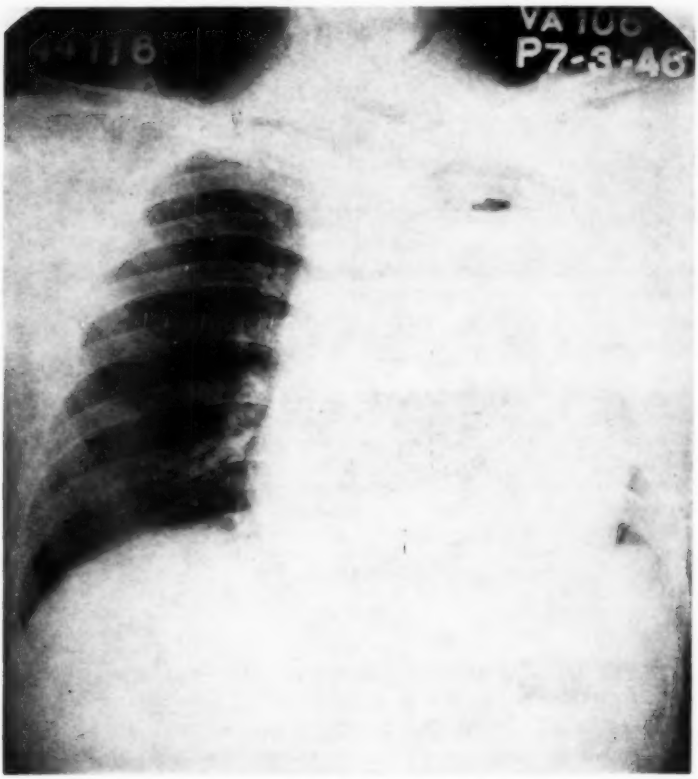

FIG. 1. Photograph of roentgen-ray before therapy.

empyema, and broncho-pleural fistula. In their review of the literature, Finland et al. mention five cases of putrid empyema that were treated with intrapleural penicillin instillations without surgical drainage. Of these five cases, two were cured. In these two cases the putrid empyema was further complicated by the presence of broncho-pleural fistulae.

The following case is of interest in that, in spite of putrid empyema contents

and a broncho-pleural fistula, the patient made a surprisingly prompt and uneventful recovery under intensive penicillin therapy. The patient received intramuscular penicillin, penicillin aerosol, and intrapleural instillations of penicillin.

The concomitant existence of a broncho-pleural fistula, in the cases of putrid empyemas successfully treated medically, demonstrates that such a fistula can

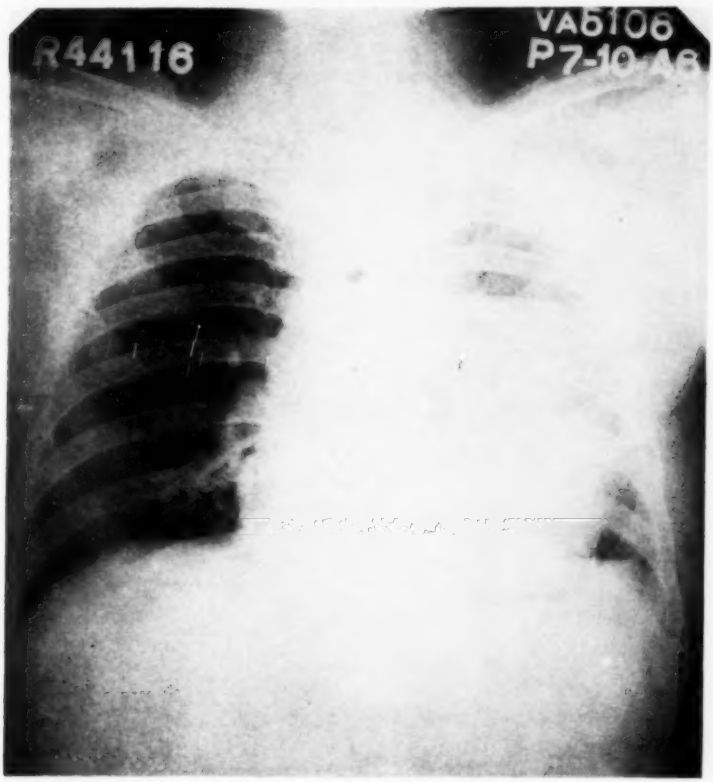

FIG. 2. During therapy.

heal without open drainage if the infection can be controlled. It also suggests that the fistula might have served a useful purpose in emptying the empyema cavity.

CASE REPORT

A 52 year old farmer first became ill during the last week of May, 1946. At this time he noted a sudden onset of chills and fever subsequent to the extraction of three abscessed teeth. The following day he had severe, anterior left chest pain on

respiration. He was told by his physician that he had pleurisy and was given penicillin intramuscularly every four hours for six days. The chest pain subsided but his fever persisted. He had only a slight cough at this time.

On June 4 he was admitted to a local hospital with complaints of fever, weakness, anorexia, and weight loss. A diagnosis of probable pulmonary abscess was made at that time. Treatment consisted of intramuscular penicillin for two weeks and a course of a sulfonamide for one week. About June 20 the patient suddenly developed a severe cough productive of large amounts of greenish sputum.

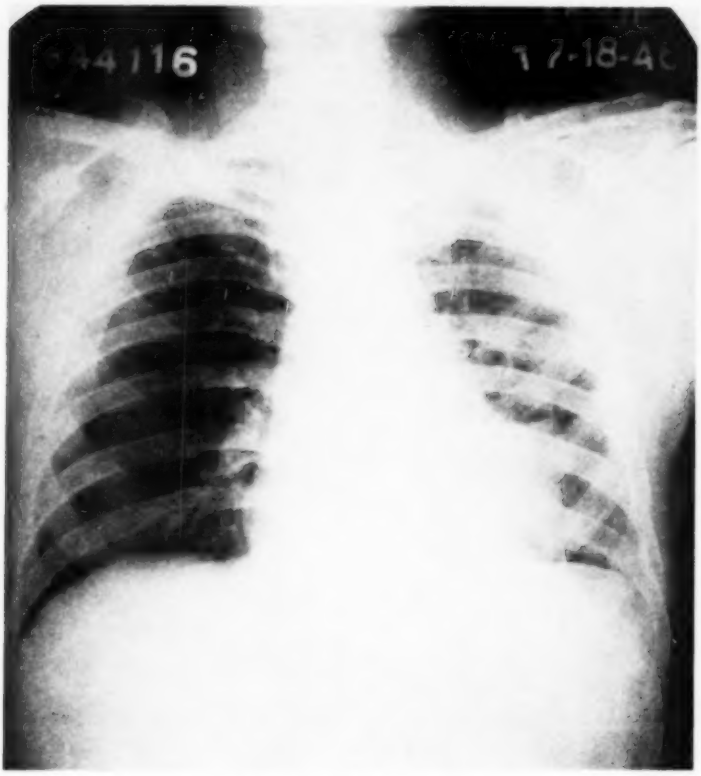

FIG. 3. During therapy.

On July 2 he was transferred to the Veterans Administration Hospital in Minneapolis. At this time his complaints included fever, productive cough, malaise, anorexia, and weakness. Physical examination revealed a well-developed 52 year old white male who showed evidence of recent weight loss. Temperature was 102.4°, pulse 104/min., respiratory rate 24/min. The patient weighed 155 pounds, in contrast to his usual weight of 185 pounds. Blood pressure was 140/82 mm. Hg. The teeth

were carious and moderately advanced pyorrhea was present. There was mucopurulent material in the pharynx. No cardiac abnormalities were noted; no organs or masses were palpable in the abdomen.

Examination of the chest revealed slight atrophy of the muscles over the left chest. The right lung was normal to auscultation and percussion. There was resonance over the left anterior lung, in the left axilla, and over the extreme upper portion of the left posterior lung. The lower three-fourths of the left posterior lung revealed dullness to flatness on percussion; tactile fremitus was decreased over this

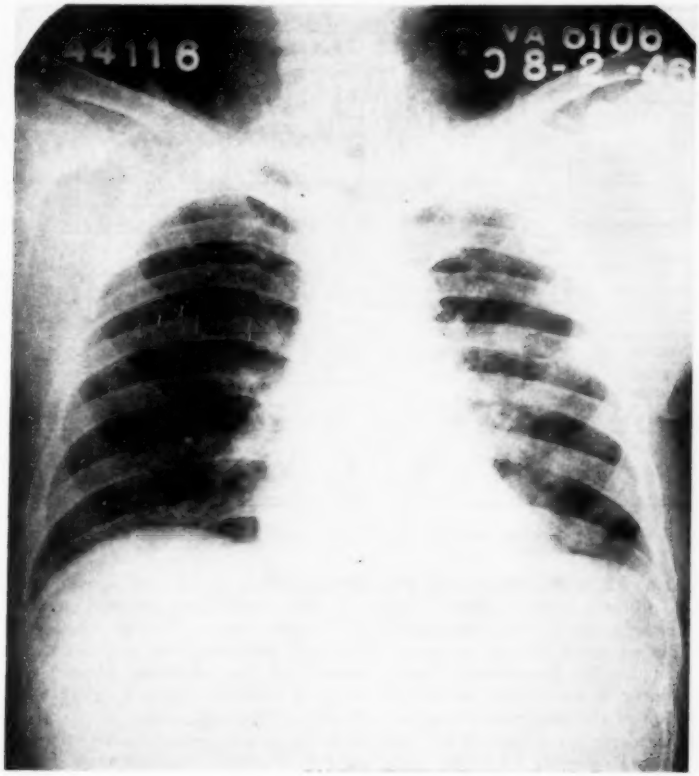

FIG. 4. After therapy.

area and the breath sounds were diminished though bronchial in quality. The sputum was green, purulent, and odorless.

Laboratory studies on admission showed the hemoglobin to be 11.8 gm., with 3,680,000 red blood cells. White count was 14,400, with 82 per cent neutrophiles, 15 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed a specific gravity of 1.015, with albumin and sugar negative. Postero-anterior chest roentgen-ray showed a density involving almost the entire left chest with an airfluid level in

the infraclavicular area. Lateral view of the chest showed the density to lie entirely posteriorly. The roentgen-ray appearance was interpreted as being suggestive of a large empyema with a broncho-pleural fistula. Sputum cultures showed the presence of coliform organisms. Vital capacity was 2.3 liters. The electrocardiogram was normal. A diagnostic thoracentesis was performed at the angle of the left scapula. Three ounces of thick, greenish, purulent material with an extremely foul odor were aspirated. Culture of this fluid revealed non-hemolytic streptococci and *Aerobacter aerogenes*.

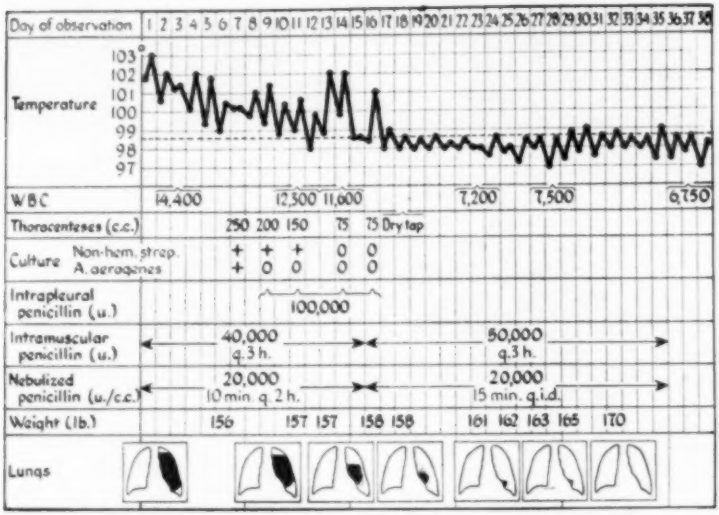

FIG. 5. Graphic summarization of the patient's course and therapy.

It was felt at this time that the patient presented the problem of a putrid empyema with a probable broncho-pleural fistula. It was decided, in conjunction with the thoracic surgeons, to defer any surgical intervention for a period of one week to 10 days, during which time an intensive therapeutic program with penicillin was to be carried out. The treatment instituted consisted of the following: 100,000 units of penicillin in 50 c.c. normal saline were instilled into the empyema cavity following aspiration of the empyema fluid every 48 hours. Forty thousand units were given intramuscularly every three hours, and penicillin was nebulized for 10 minutes each hour in concentration of 20,000 units per c.c. Postural drainage was carried out several times daily with raising of 100 to 250 c.c. of sputum daily. During the third instillation of penicillin into the pleural cavity the patient stated that he could taste the penicillin. A small amount of Evans blue dye was added and the patient promptly coughed up bright blue sputum. This definitely established the existence of a broncho-pleural fistula.

Aerobacter aerogenes was no longer cultured from the empyema fluid after the first aspiration. The non-hemolytic streptococcus persisted until after the third penicillin instillation. This organism was shown to be sensitive to 0.2 unit penicillin per c.c. in vitro.

After four penicillin instillations there was marked clinical improvement. Surgical intervention was not considered necessary. Chest roentgenograms showed marked diminution in the size of the cavity and in the amount of fluid. No fluid was obtained on thoracentesis. Intramuscular and nebulized penicillin was continued for two weeks, during which time the patient became asymptomatic and afebrile, the cough disappeared, and the white blood count fell to 7,500. The vital capacity increased to 2.9 liters. On August 1 all penicillin was discontinued. Chest roentgenray showed evidence of thickened pleura, as did physical examination, but no encapsulated fluid could be visualized. At this time the patient had gained 15 pounds since admission. The patient was discharged from the hospital on August 9, eight days after discontinuation of penicillin, no symptoms, febrile reaction, or positive physical findings having recurred.

The total period of hospitalization following diagnostic thoracentesis was four and one-half weeks.

Fifteen weeks after discharge from the hospital the patient was entirely asymptomatic and engaged in his normal farming activities.

Conclusion

A case is presented demonstrating the cure of a putrid empyema with a broncho-pleural fistula obtained with penicillin therapy.

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EDITORIAL

THE ELECTROENCEPHALOGRAM

THE recent appearance of Electroencephalography and Clinical Neurophysiology ("The EEG Journal") under the auspices of the International Federation of EEG Societies serves to emphasize the growth and the increasing importance of this highly specialized field of medicine. Almost everyone has heard of the "brain waves" and is aware that they are used in diagnosis. Many, however, even among physicians, do not know precisely in what disorders the EEG is really useful in diagnosis and particularly are not aware of its present limitations. Some knowledge of the nature of the observations on which conclusions are based, as well as of sources of error both in technic and in interpretation, may help to clarify the subject.

That changes in electrical potential accompany cortical activity has been known for many years. Thus Caton (1875), working with the exposed brain of experimental animals, noted "feeble currents of varying direction" when electrodes were placed on two points of the external surface. To detect and usefully record these differences on the scalp, where their amplitude is greatly reduced, was impossible until technical methods of amplification had been perfected. Berger (1929) was the first to accomplish this, but at first his observations were distrusted, and they were not confirmed until 1934 by Adrian and Matthews.

In a tracing from a normal adult, amid the apparent jumble of waves one may make out in the relaxed waking state sequences of similar rhythmic waves of two characteristic types. The alpha waves appear as smooth waves with a rounded tip, of moderate amplitude (average about 35 microvolts) and at a frequency of about 8 to 12 per second, dominant occipitally. Normally these are usually synchronous and about equal in amplitude in symmetrical areas in the two hemispheres. Less often there are series of "low voltage fast" activity, beta waves, with an amplitude of about 10 microvolts or less and a frequency of 18 to 30 per second, dominant centrally.

The occurrence of such waves shows clearly that the cortical cells do not "discharge" in a haphazard fashion but that large numbers of them discharge in unison in a regular rhythmic manner. A disturbance of such rhythmic sequences is often referred to as cerebral dysrhythmia. The exact mechanism of the production of these electrical changes is not known. Normal activity of the cortical cells is essential, but there is good reason to believe that it is at least regulated by deeper structures, possibly the thalamus. They may be affected by physiological cerebral activity. Thus alpha waves tend to be depressed or abolished by mental concentration or visual stimulation, and this factor must be considered in the interpretation of the records.

The alterations in the tracings which are observed in pathological conditions may be of several different types. There may be a general dis-

organization of the pattern with loss of the regular sequences of rhythmic waves. The amplitude may be increased or diminished. There may be bilateral asymmetry, either in frequency or amplitude, of the waves. There may be "slow" waves (less than 8 per second), either isolated "random" waves, focal or diffusely scattered over the head; or such waves may come in regular sequences which are of great significance, especially if their amplitude is high. "Spikes" may occur, similarly distributed, brief, sharp-tipped waves, often of high amplitude.

Finally there is the well known "wave-and-spike" or "spike-and-dome" pattern, usually occurring in regular rhythmic series and generalized. This is always found during a clinical petit mal seizure, is often present in such cases in intervals between clinical seizures, and occurs occasionally between seizures in patients with convulsive attacks in whom no clinical petit mal seizures have been recognized. Although virtually pathognomonic of idiopathic epilepsy, this pattern has been reported as a sequel of encephalitis in children.

The first major application of the EEG to clinical diagnosis and perhaps the most important was in epilepsy, following the observations of Lennox and Gibbs. Immediately preceding a grand mal seizure highly characteristic changes occur, consisting often of numerous spikes associated with and eventually replaced by a generalized sequence of rhythmic slow waves of high amplitude. In the interval between seizures in some cases there are occasional short sequences ("bursts") of spikes, rhythmic slow waves, or both. Quite frequently there are only random scattered slow waves which are abnormal but not in themselves diagnostic, and in about 15 per cent of the cases no clear cut abnormality can be found.

The wave-and-spike pattern of the petit mal seizures has been noted. In "psychomotor epilepsy," episodes of abnormal behavior regarded by some as an "epileptic equivalent," Gibbs has described slow, notched or flat-topped waves, but others have questioned their significance as a manifestation of epilepsy.

Finally there is a group of clinically normal individuals, according to some constituting up to 15 per cent of the population, whose records show non-specific abnormalities, usually of minor degree.

Focal destructive lesions involving the cortex, including tumors, abscesses, local traumatic lesions, subdural hematomata and scars resulting from such lesions, cause definite abnormalities in many cases. The commonest manifestation of superficial cortical lesions is the occurrence of random slow waves, generally not equal or rhythmic, which are usually localized. More rarely there may be spikes alone or a mixture of spikes and slow waves, but only if the electrode is close to the tumor. There may be a similar disturbance in the symmetrical area on the other side but usually of lower amplitude. The abnormal waves do not arise from the tumor, which electrically is relatively "dead" tissue, but from the damaged cortex at the margin of the tumor. In the case of deep tumors the disturbance may be generalized.

Walker has used this procedure to localize lesions (especially epileptogenic foci) precisely by applying electrodes to the exposed cortex and determining the exact area from which spikes arise. This can rarely be accomplished over the scalp, and other devices must be employed. One such is the demonstration of a "phase-reversal" of the electrical potential in the region of a tumor. If simultaneous tracings are taken with a series of electrodes arranged in a semicircle about the head and passing over or near the tumor, a distinctive abnormal wave may have a negative potential as one approaches the tumor and a positive potential as one passes away from it.

There are no criteria by which the various types of focal lesions can be distinguished with certainty by the EEG. The latter merely indicates a focus of abnormal electrical activity associated with injured cortical tissue. A more precise diagnosis can often be reached, however, in conjunction with the clinical history and the results of a neurological examination and other special procedures. Negative findings do not exclude a focal lesion.

The EEG is a valuable means of detecting cerebral damage following head injuries. In the acute stage, if the injury was severe and brain tissue damaged, abnormalities can almost always be demonstrated. These may closely resemble those seen in idiopathic epilepsy, but they have no prognostic significance unless they persist. In that event convulsive seizures eventually are prone to develop. In general these abnormalities tend to disappear gradually during the first six months, and in most cases largely or completely by the end of a year. Lesser changes may persist indefinitely, however, such as disorganization of the wave patterns, scattered slow waves, and depression of alpha waves, usually on the affected side. Similar changes are seen occasionally in clinically normal persons, and it has been suggested that they may be sequelae of unrecognized head injuries in childhood. In the cases with minor contusions or mild degrees of concussion there are usually no abnormalities.

The EEG has also been used in a study of degenerative processes such as cortical atrophy, porencephaly, and infarcts. In cases of longstanding hemiplegia there is usually but little abnormality in ordinary records. In sleep records, however, depression of the fast component has been reported, and also a reduction in the response to auditory stimulation on the affected side.

In acute encephalitis there are always abnormalities which gradually disappear unless cortical injury is severe.

Metabolic disorders may also cause alterations in the EEG. Hypoglycemia in a degree insufficient to cause clinical symptoms may cause changes which could be mistaken for epilepsy or organic cerebral disease. These can be eliminated by administration of glucose.

In the neuroses and ordinary functional psychoses the EEG has been of no positive value in diagnosis. No distinctive changes have been recognized, and the proportion of cases showing nonspecific abnormalities is no greater than in the general population.

As already noted, normal records are obtained in a significant percentage of patients with epilepsy or organic brain disease. Various procedures have been tried to elicit abnormalities in such cases, of which hyperventilation is the most useful and is now practically a routine procedure. Even in normal individuals, however, and particularly in children it tends to cause disorganization of the pattern and slowing of the activity, and care must be used in the interpretation. Injections of metrazol have been used, but the technic has not been adequately standardized.

Sleep or drowsiness causes marked changes in the EEG, depending upon the depth of sleep. The most important are a general slowing of the rate and the appearance of irregularly distributed slow waves of high amplitude which may be interpreted by the unwary as indications of disease. There is also a fast component, sequences of waves at 12 to 14 per second that often appear in the form of "spindles."

Records taken during sleep often yield information not obtained in waking records, particularly if they include shifts between the waking and sleeping state. Sleep may be natural or induced by hypnotics, of which seconal seems at present to be the most satisfactory. The characteristic changes in epilepsy may often be induced in this way; these are not masked by sleep, but they can be more easily recognized. Sleep markedly lessens the artefacts in the records due to gross muscular movement or tension, and it may be the only way of obtaining records in hyperkinetic or unruly children.

To be of value it is essential that the test be carried out with meticulous care by a thoroughly trained technician. The requirements in this respect are far more exacting than for any of the other diagnostic procedures in common use. Artefacts arising from technical errors or mechanical defects in the apparatus may simulate almost any of the pathological alterations that have been described. Particularly disturbing are spikes and waves of increased amplitude, either scattered or in sequence. Among the commoner sources of trouble are poorly applied or loosened electrodes, improperly placed electrodes, spread of electrode paste, sweating, swaying of the electrode wires, restless movements of the patient, blinking of the eyes, unrecognized drowsiness, faulty or "noisy" vacuum tubes and static electrical disturbances arising from sparking motors, diathermy or roentgen-ray machines. Tension or twitching of the cranial muscles, especially the temporals, causes "muscle spikes" which may obliterate other features of the tracing or, if sparse, may be mistaken for spikes of cortical origin.

The individual who interprets the record must be familiar with these artefacts and differentiate them from significant alterations. This is not always easy. He must be familiar with the standards of normal, which vary with age. In normal infants the records are poorly organized and show predominantly irregular slow activity. The shift to the adult pattern is gradual and is not usually attained until the fourteenth to eighteenth year. The record of any normal child is, therefore, likely to show aberrations from the adult pattern which would be pathological in an older age group.

He must be familiar with the degree of abnormality which may be anticipated in certain clinically healthy individuals. There is no general agreement as to this, and it is impossible to distinguish sharply between normal and abnormal records. If the criteria of normal are made so strict as to exclude most of the "false negatives," a disturbing number of misleading "abnormal" records will be obtained. In general the abnormalities in these "border-line" records should be regarded as of no diagnostic significance in themselves. In a patient with known or suspected disease, they may have some confirmatory value if they are characteristic, and they indicate the need for repeated tests and possibly special procedures to secure more definite information.

Finally, the individual who interprets the record must have all the information available regarding the patient if the test is to be really useful and dependable. With the possible exception of a minority of the cases of idiopathic epilepsy, it is rarely if ever possible to make a conclusive diagnosis on the basis of an EEG alone. It is often of great value in differential diagnosis, however, in cases of organic disease in which the nature of the lesion is in doubt; e.g., if there is a question as to epilepsy, tumor or a traumatic lesion.

If the referring physician lacks the technical knowledge and experience required to interpret the record himself, this clinical information must be supplied to the one making the test. For example, patients who have received treatment with electroshock show sequences of slow waves of high voltage which gradually disappear after treatment is stopped but may persist in some degree for six months to a year. If this is not known, a gross misinterpretation is likely to result. Furthermore, if this information is available before the test is carried out, it often helps greatly in selecting those procedures most likely to reveal abnormalities in a given case. To withhold information in order to secure an unbiased opinion defeats its own purpose.

An EEG, therefore, furnishes information of great diagnostic value in many suitably selected cases, if it is properly made and interpreted with discrimination in conjunction with all the other information available.

P. W. C.

REVIEWS

Clinical Allergy. By Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia, Pennsylvania. Second edition. 690 pages; 16 × 24 cm. Lea and Febiger, Philadelphia 6, Pennsylvania. 1949. Price, $12.00.

In the opinion of this reviewer, Dr. Tuft's book is the best text on allergy available. The present volume is planned along lines similar to those followed in his original, or previous edition. However, it has been thoroughly rewritten and is modern in every sense. The volume is attractive in appearance, is a reasonable size, the type is clear, and the subject matter well arranged.

The author has retained his basic method of presentation in that the major divisions of the text are unchanged. First, general considerations of allergy are presented with a satisfactory discussion of the basic facts of anaphylaxis and allergy. This serves as an adequate orientation for the uninitiated and, in addition, will bring the practicing allergist abreast of current thinking about important phases of these subjects. The author then discusses etiological agents in groups, pointing out the important group characteristics of different types of allergens and calling attention to the clinical significance of these facts.

His discussion of the clinical manifestations of allergy, that is, the conditions one must treat practically, is sound, complete, and sufficiently free from confusing speculation to make it of great value in the clinical application of the vast amount of data his book contains.

In his discussion of the treatment of asthma, those of us who have used Butanefrine extensively will be disappointed to find no mention of this very valuable drug; particularly, when one considers the space given to other agents of doubtful value, some of which he condemns. This omission is difficult to understand.

This volume is a textbook in the best sense of the word. It is sufficiently dogmatic to permit the reader to chart a course clinically. Pertinent facts are given, doubtful data have been omitted. The author, also, avoids the temptation to coin new phrases and to add new classifications to the multiplicity of these now extant that dog the beginner in his attempt to see different phases of allergy clearly and with understanding.

Brief summaries of the different sections are again introduced with profit as are the comparative tabulations of differential diagnostic criteria in those conditions showing confusing similarities.

The section in which data are given on the place of occurrence of allergens and the technical procedures peculiar to allergy, is most valuable.

The newly included material on molds and antihistaminics is excellent and is presented with brevity and clarity as is usual with this author. However, the omission of the excellent bibliography included in the original edition represents a distinct loss, and it is unfortunate that the publishers deemed this necessary.

This book will be of great service to all physicians desiring to increase their knowledge of allergy. This should include all members of the profession.

H. M. B.

Clinical Auscultation of the Heart. By SAMUEL A. LEVINE, M.D., Clinical Professor of Medicine, Harvard Medical School; Physician, Peter Bent Brigham Hospital; and W. PROCTOR HARVEY, M.D., Research Fellow in Medicine, Harvard Medical School, Assistant in Medicine, Peter Bent Brigham Hospital. 327 pages; 15 × 23.5 cm. W. B. Saunders Co., Philadelphia. 1949. Price, $6.50.

This text deals with the information that can be obtained by the use of the stethoscope, "such an inexpensive and expedient tool." It contains many interesting and valuable details concerning both normal and abnormal heart sounds. For example, the authors point out that the first heart sound may be accentuated when the P-R interval is shorter than normal, because of the position of the A-V valves so soon after auricular contraction. They describe the "inching procedure" to differentiate systolic from diastolic gallop sounds. They state that in general the sounds of an auricular premature beat resemble the normal beats of that particular patient and that the sounds of a ventricular extrasystole are different. There is some confusion when the authors attempt to differentiate between the normal third heart sound, the opening snap of mitral stenosis, and the protodiastolic gallop sound. The important problem of the diagnosis of rheumatic mitral insufficiency in the absence of mitral stenosis is solved by basing the diagnosis not upon the intensity of the murmur alone, but also upon the history, the presence of some cardiac enlargement and an abnormal fluoroscopic appearance of the left auricle.

In general the descriptive material can be read with interest and profit. The caption for figure 240 is incorrect, and should read "subaortic stenosis" rather than "subacute stenosis." The book is abundantly illustrated with 286 figures, chiefly stethograms which do not equal the written text in quality. There are 35 pages of index for the 291 pages of text and figures. It is regrettable that this book, which brings together much information concerning auscultation of the heart, contains no bibliography to which the reader may refer for the basic studies in this important field.

S. S.

Correlative Neuroanatomy. By J. J. MCDONALD, J. G. CHUSID, and J. LANGE. 156 pages; 17.5 × 25 cm. University Medical Publishers, P. O. Box 761, Palo Alto, Calif. Fourth edition, revised. 1948. Price, $3.00.

It is not a simple matter to determine what actual value a book such as "Correlative Neuroanatomy" has. It is in the nature of such a compendium that the dynamics of the subject be excluded, for all of the data have to submit to precise definition and classification. Obviously, "Correlative Neuroanatomy" has been written for the medical student, or perhaps the young physician who is not a trained neurologist. If its purpose is to permit the hasty and transitory memorization of sufficient data to enable one to pass an examination, then it is not a failure. However, if the authors intended that their publication be used, in place of the several textbooks to which they refer so freely, for the purpose of really teaching fundamental neurology, they have not succeeded. It is in that essential lack of a dynamic approach that they fail. For it is only when one has a grasp of the dynamics of a subject, as the pathogenesis of a disease, that one knows the subject and does not have to memorize pre-arranged data. Actually the material contained in "Correlative Neuroanatomy" is readily available in standard texts, in which dynamics are given due consideration. If this condensation of neurology fails the medical student, it surely is of little value to the trained neurologist.

In addition to its general inadequacy, "Correlative Neuroanatomy" is not without some significant errors. Some of the latter may well be a result of the necessity to condense the material. A number of the inaccuracies will be pointed out. Under cranial nerve II various visual defects are listed, among them the entity, "optic agnosia—(word blindness)—cannot name objects seen—angular gyrus lesion." It is

hardly correct to classify an agnosia among the cranial nerve lesions, even though it is qualified by the reference to the angular gyrus. Actually "optic agnosia" and "word blindness" are not synonymous. On page 7 one finds the statement, "circumferential blindness ('tubular vision') due to hysteria or retrobulbar neuritis." Retrobulbar neuritis notoriously causes a central scotoma and not a constriction of the peripheral fields. Under cranial nerve VIII the authors include, "sensory aphasias—(word deafness)," and "auditory hallucinations" as "symptoms of VIII nerve involvement." Similarly, "motor aphasia" is incorrectly listed among the "symptoms and signs of vagal involvement," as are "psychogenic disturbances." The latter are also included under the cranial nerves XI and XII. Psychogenic disturbances, aphasia, and agnosia involve disturbances of the cerebral cortex, and not of the cranial nerves.

Since this text has been planned to be concise, why the authors pay so much attention to the antiquated terminology commemorating the many pioneers in neurology is hard to understand. Many of the names listed are rarely used. Would it not be best to discourage their employment by omitting them, and using more meaningful designations, even if longer? For instance, under progressive muscular atrophies, among the bulbar types a "Fazio-Londe" syndrome is referred to. Wilson in his encyclopediac text merely refers to these two authors among many others who have described cases of subacute bulbar palsies. Also, why is it necessary to refer to the resistance to stretching the brachial plexus in neuritis of the latter, as Bikele's sign?

While the definitions of many terms are well done, the thumb-nail descriptions of the various disease entities and tumors are hardly sufficient for the beginner, and surely unnecessary for the initiate.

Perhaps the reader harbors a peculiar bias against compendia that make available skeletal material that can be exploited by those who are disinclined to make a more thorough study of neurology, no doubt "Correlative Neuroanatomy," barring its errors, has served many a medical student well in helping him prepare for examination.

H. A. T.

Obstetric Analgesia and Anesthesia. By FRANKLIN F. SNYDER. 401 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1949. Price, $6.50.

From the author's rich background of clinical and experimental investigation comes this interesting compilation of data concerning the various agents used in obstetrics to produce analgesia and anesthesia. The analysis of the physiologic and pharmacologic factors together with the survey of clinical case reports and conclusions, seemed to the reviewer to be particularly unbiased.

The work is divided into two sections, the first of which, comprising about half of the book, is a rather technical but clear exposition of fetal respiratory physiology and pathology, which proposes to prove that the fetal respiratory system is the site of greatest vulnerability to injury that proves fatal during labor or following it. It is also shown that intrauterine respiratory activity, like that seen after birth, takes place. Thus, breathing begins far back in embryonic life. It is indicated that since the functional significance of fetal respiration has been established, a new approach is open to the analysis of the hazards of labor to the child. The author describes much of his own fundamental experimental work on fetal respiratory physiology including assay of the pharmacologic factor in labor as illustrated by the action of various drugs in obstetric analgesia. He uses fetal respiratory movements as a sensitive indicator which can detect the earliest effect of narcosis. Results are expressed in terms of depression in activity of the fetal respiratory system and by impairment in the effective uterine expulsive mechanism. The first section is a background for the more clinical second section.

In his introduction to the second section, the author states his belief that how much pain relief can be attained for the mother and how little risk is involved for the child, are matters that can hardly be settled by clinical impressions alone. Thus, in evaluating each analgesic or anesthetic agent, he determines its potency in the relief of pain, its effect upon the fetus and its effect upon the mother, especially upon the labor mechanism. In the chapter on regional anesthesia, the results of the use of various agents in the conduct of labor are presented from the standpoint of the method of administration rather than from that of the action of a given drug.

The book is attractively printed, serviceably bound, and an extensive bibliography is found at the end of each chapter. There is an excellent summary concluding most of the chapters. The illustrations are clear and well-chosen. There is an adequate index. To all who practice obstetrics, this book will be found most interesting and helpful.

J. E. S.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Autobiography of Dr. Robert Meyer (1864–1947): A Short Abstract of a Long Life. With a Memoir of Dr. Meyer by EMIL NOVAK, M.D. 126 pages; 26 × 17.5 cm. 1949. Henry Schuman, New York. Price, $2.50.

Die Bazillenruhr. By LUDWIG ROEMHELD. 125 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $3.25.

Blakiston's New Gould Medical Dictionary: A modern comprehensive dictionary of the terms used in all branches of medicine and allied sciences, including medical physics and chemistry, dentistry, pharmacy, nursing, veterinary medicine, zoology and botany, as well as medicolegal terms; with illustrations and tables. 1st Ed. Editors: HAROLD WELLINGTON JONES, M.D., NORMAND L. HOERR, M.D., and ARTHUR OSOL, Ph.D., with the coöperation of an Editorial Board and 80 contributors. 1294 pages; 25.5 × 17.5 cm. 1949. The Blakiston Company, Philadelphia. Price, $8.50.

Blood Transfusion. By H. F. BREWER, RICHARD ELLIS, R. I. N. GREAVES, GEOFFREY KEYNES, F. W. MILLS, R. BODLEY SCOTT, ANTHONY TILL and LIONEL WHITBY; Edited by GEOFFREY KEYNES. 574 pages; 22.5 × 15 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $12.50.

Bridges' Dietetics for the Clinician. 5th Ed. Edited by HARRY J. JOHNSON, M.D., F.A.C.P., Formerly Assistant Clinical Professor of Medicine, New York Post Graduate Medical School, etc. 898 pages; 24 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, $12.00.

Darmbrand Enteritis Necroticans. By K. HANSEN, E. JECKELN, J. JOCHIMS, A. LEZIUS, H. MEYER-BURGDORFF and F. SCHUTZ. 212 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $7.50.

Diagnostische und Therapeutische Eingriffe des Internisten: Vorbereitung, Technik, Komplikationen und Gefahren. By DR. MED. EBERHARD REGENBOGEN. 262 pages; 21 × 15 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $4.50.

Differentialdiagnose der Inneren Medizin. 3. Unveränderte Auflage. Herausgegeben von Seinen Schülern. By NAEGELI. 794 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $9.00.

Einführung in die Innere Medizin. By Dr. Hans Julius Wolf. 608 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $7.25.

Das Ekg-ABC: Eine Systematik zur Auswertung von Elektrokardiogrammen. By Max Waldhecker. 114 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $2.25.

Die Erkrankungen des Darmes. Anhang: Die Prokto-sigmoidoskopie. By Walter Zweig (London). 253 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $6.75.

Grundlagen zur Erforschung des Alterns. By Dr. Paul Matzdorff. 248 pages; 23.5 × 15.5 cm. 1948. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main, Germany. Price, DM 13,50.

Die Insulin-lipodystrophie. By Prof. Dr. Ferdinand Adalbert Kehrer. 50 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $1.50.

Die Konstitutionellen Vergrosserungen Umschriebener Korperabschnitte. By Prof. Dr. Ferdinand Adalbert Kehrer. 293 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $8.50.

Lehrbuch der Haut- und Geschlechtskrankheiten. By Dr. Walther Schönfeld. 467 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $7.25.

Lehrbuch der Klinischen Hämatologie. By Professor Dr. Hans Schulten. 499 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $11.00.

Leitfaden der Blutmorphologie. By Lydia Schudel. 47 pages; 24.5 × 17 cm. (paper-bound). 1947. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $3.00.

Die Lungentuberkulose. By Prof. Dr. Med. H. Gissel and Dr. Med. Habil. P. G. Schmidt. 264 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $8.00.

Marihuana in Latin America: The Threat It Constitutes. By Pablo Osvaldo Wolff, M.D., Ph.D., M.A., Buenos Aires, Argentina, Member of Expert Committee on Habit Forming Drugs of the World Health Organization. 56 pages; 20.5 × 13.5 cm. (paper-bound). 1949. Sponsored by Washington Institute of Medicine; published by The Linacre Press, Inc., Washington, D. C. Price, $1.50.

Medizinische Klinik ein Fortbildungskurs für Ärzte. By Prof. Dr. Ferdinand Hoff. 467 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $9.00.

Modern Practice in Psychological Medicine—1949. Edited by J. R. Rees, M.D. 488 pages; 25 × 17 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Neuere Tuberkuloseforschung I. By Obermedizinalrat Dr. Griesbach, Augsburg. 112 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $2.00.

Outlines of Internal Medicine. 6th Ed., First Printing. Edited by C. J. Watson, M.D., Head, Department of Medicine, University of Minnesota. First four

parts of volume, 434 pages; fifth part of volume, 94 pages; 29 × 22 cm. 1949. William C. Brown Company, Dubuque, Iowa. Price, $12.00.

Die Pathologisch-anatomischen Grundlagen der Allergie. By Doz. Dr. Med. Wilhelm Eickhoff. 95 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $2.50.

Pathologische Physiologie der frischen, geschlossenen Hirnverletzung, insbesondere der Hirnerschütterung; klinische, anatomische und experimentelle Befunde. By R. Wanke. 200 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $7.25.

Rational Medicine. By John W. Todd, M.D. (Lond.), M.R.C.P. (Lond.), Assistant Physician to Farnam Hospital, etc. 378 pages; 22.5 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $6.50.

Rehabilitation of the Handicapped: A Bibliography, 1940–1946 (in two volumes). By Maya Riviere. Total pages in both volumes, 998; 24 × 15.5 cm. 1949. National Council on Rehabilitation, New York. Price, $10.00.

Rh-Syllabus. By Alexander S. Wiener, M.D., F.A.C.P., F.C.A.P. 28 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $0.75.

Die Technik der Blutgruppen- und Blutfaktorenbestimmung. By Dr. Med. Habil. Peter Dahr. 250 pages; 21 × 15 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $3.75.

Textbook of Medical Treatment. 5th Ed. By Various Authors. Edited by D. M. Dunlop, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), Professor of Therapeutics and Clinical Medicine, University of Edinburgh, etc.; L. S. P. Davidson, B.A. (Camb.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), M.D. (Oslo), Physician, H.M. The King in Scotland, etc., and J. W. McNee, D.S.O., D.Sc., M.D. (Glas.), F.R.C.P. (Edin.), F.R.C.P. (Lond.), Physician, H.M. The King in Scotland, etc. 999 pages; 24.5 × 17.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $8.50.

A Textbook of Neuropathology, with Clinical, Anatomical and Technical Supplements. By Ben W. Lichtenstein, B.S., M.S., M.D., Associate Professor of Neurology, University of Illinois College of Medicine, etc. 474 pages; 25.5 × 16.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $9.50.

Die Tuberkulose des Kindes: Ein Lehrbuch aus der Kinderheilstätte Wangen im Allgäu. By Dr. Med. Habil. Heinrich Brügger, Dr. Med. Habil. Reiner W. Müller, and Dr. Maria Birkenfeld. 340 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $5.00.

Tuberkuloselexikon für Ärzte und Behörden. By Dr. Med. Habil. Wilhelm Roloff. 372 pages; 19 × 12.5 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $4.50.

Über Weichteiltuberkulose (Tuberculosis colliquativa profunda). By Dr. Med. Maria Birkenfeld. 45 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $2.00.

Weitere Fortschritte in der Blutgerinnungslehre. By Prof. Dr. Med. Karl Lenggenhager. 243 pages; 24.5 × 17 cm. 1949. George Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, $5.50.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses

A schedule of the courses is repeated on the inside back cover page of this journal.

Although Course No. 1, Cardiology, at the National Institute of Cardiology of Mexico, had a registration of only twenty-five, due to the lateness of the announcement of the course, it was received with enthusiasm. Quoting from some of the reports received from those in attendance: "I spent a very profitable two weeks. The course was well-organized and well-conducted. I was very favorably impressed with the well-trained group of men there. The course gave me just what I wanted."—M.D., Tennessee. "In my opinion, it was the best course in Cardiology which it has been my privilege to attend. Its strong points were (1) the care with which the program was arranged; (2) the coördination between the Director and the heads of each department; and (3) the high level of instruction which each speaker maintained."—M.D., California. "A most profitable course and enjoyable vacation. The course is highly recommended, especially for catheterization technics and angiocardiography."—M.D., Texas. "The course was excellent beyond description. The courtesy of the staff and the zeal and interest of each participant has set a goal difficult to equal."—M.D., New York. "The program arranged by Dr. Chavez was informative and illuminating. Not only will the scientific program be forever remembered but likewise the hospitality of the Director. May I add that the enthusiasm and good fellowship displayed by Dr. George Morris Piersol, Dr. William Dock and Dr. George C. Griffith, American College of Physicians' guests, were deeply appreciated. I wish to express due thanks to The American College of Physicians for granting such opportunities to its members."—M.D., Pennsylvania.

When the course in Cardiology in Mexico is repeated, it is hoped that adequate notice of perhaps six or more months will be given to all members of the College, so that they can take advantage of this outstanding course.

Courses No. 2 and No. 3, Gastro-Enterology at the University of Chicago, and Clinical Neurology at Jefferson Medical College of Philadelphia, respectively, will have been concluded before the publication of this news item. In each case the registrations were reasonably large and representative. Reports from the men registered are not yet available, but from former experience it can be stated, with assurance, that no better courses in the respective fields could be arranged anywhere. Both courses have been given previously with signal success.

Those wishing to register for the remaining courses on the schedule should do so without further delay. Course No. 6, The Biological and Physiological Approaches to Internal Medicine, at the University of Wisconsin Medical School, is already registered to capacity and some of the other courses are approaching that point. Especially do Courses No. 7 and No. 8, Blood Dyscrasias, at the Medical College of Alabama, and The Physiological Approach to Clinical Problems in the Cardiovascular Diseases, at the University of Southern California School of Medicine, respectively, warrant increased registration, because there are still ample facilities available. Detailed outlines of all courses can be obtained from Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Research Fellowships of the American College of Physicians

Some months ago The American College of Physicians announced a limited number of Fellowships in Medicine and/or Pediatrics available from July 1, 1950

through June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend varies from $2,200 to $3,200 per annum, according to circumstances.

In previous years, there has been a large number of applicants for these Fellowships. This year the number has greatly decreased.

Application forms may be obtained from the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. They must be submitted in duplicate by an early date in October. Announcement of awards will be made following the Board of Regents meeting on November 13, 1949.

A.C.P. Committees and Regents Meet November 11–13, 1949

The regular Autumn meetings of the Board of Regents and their various committees will be held at the Headquarters of the College in Philadelphia, November 11–13, 1949. At this time Research Fellowships for 1950–51 will be awarded; the postgraduate program for 1950 will be adopted; candidates for membership, presented prior to September 12, 1949, will be passed on, and other essential business of the College transacted.

The next succeeding meeting of the Committee on Credentials for the consideration of candidates will be held at Philadelphia on or about March 19, 1950.

The next Annual Session of the College will be held at Boston, Mass., April 17–21, inclusive, 1950. General Headquarters, Mechanics Building; Hotel Headquarters, The Statler and Copley Plaza Hotels. All reservations will be handled through a Housing Bureau, conducted by the Boston Convention Bureau.

A.C.P. Directory, 1949

The new and revised Directory of The American College of Physicians is progressing toward completion; but the revisions were so extensive that the publication date has been delayed beyond that originally anticipated. It is confidently hoped that it will be mailed during November to those who placed orders. The pre-publication price was $4.00. Members will be billed after delivery of their copy to them. For those who have not previously placed orders, the post-publication price is $5.00.

Grateful acknowledgment is made of the receipt of the following publications from Fellows of the College:

"Dorothea Lynde Dix: America's Greatest Woman," Frederick R. Taylor, M.D., F.A.C.P., High Point, N. C.

"Three Suggestions for Medical Graduates," Paul F. Whitaker, M.D., F.A.C.P., Kinston, N. C.

Postgraduate Course in Diseases of the Chest

A Postgraduate Course in Diseases of the Chest is announced by the Council on Postgraduate Medical Education of the American College of Chest Physicians to be

held at the Hotel New Yorker, New York City, November 14–18, 1949. The announcement states that the course is given with the coöperation of members of the staffs of the New York City medical schools and hospitals. Fee for the course is $50.00. Information can be obtained from the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

Postgraduate Course in Cardiology at Dallas

A postgraduate course in Cardiology presented under the coöperation of the Dallas Academy of Internal Medicine, the Dallas Heart Association and the Faculty of Southwestern Medical School will be conducted at Dallas, November 28—December 1, 1949. The course will be held at the Melrose Hotel and Parkland Hospital. Applications for registration should be sent to the Dallas Southern Clinical Society, 433 Medical Arts Bldg., Dallas 1, Tex.

Course in Clinical Cytology

McGill University and the Royal Victoria Hospital, Montreal, announce a two-weeks course in individual instruction in Cytological Technics and Interpretation, November 7–21, 1949, under the direction of Dr. J. Ernest Ayre. The tuition fee is $100.00.

Research Grants and Fellowships to Be Made Available in 1950 by the Life Insurance Medical Research Fund

Applications for 1950 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $550,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1950–51 will also be received by this Fund up to January 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available.

New grants and fellowships will become available on July 1, 1950.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available on request.

Federal Grants for Nationwide Attack on Heart Disease

The United States Public Health Service and the National Heart Institute recently announced grants of federal funds amounting to $8,614,737 to 85 medical schools and research institutions in 34 states and the District of Columbia. Admin-

istered by the National Heart Institute of the Public Health Service, the funds will be used for stepped-up heart research, for expanded programs of heart teaching in medical schools, and for building additional heart research laboratories throughout the country.

Medical Schools Receive Kellogg Grants

Grants for medical education amounting to nearly a quarter of a million dollars have been announced by the W. K. Kellogg foundation, the University of Oklahoma School of Medicine to receive $130,000 over a period of five years and Emory University School of Medicine, Atlanta, to receive $110,000. The grants are intended to help support certain programs which these medical schools have begun or will place in operation during the present academic year.

The Interstate Postgraduate Medical Association of North America will hold its Thirty-fourth International Medical Assembly at Philadelphia, October 31–November 3, inclusive, 1949, under the presidency of Dr. Evarts A. Graham, F.A.C.S., of St. Louis and the general chairmanship of Dr. Richard A. Kern, F.A.C.P., President of the Philadelphia County Medical Society and Professor and Head of the Department of Medicine, Temple University School of Medicine.

Annual "Home-Coming" at Pottenger Sanatorium

For many years friends and former patients of Dr. Francis M. Pottenger, Sr., F.A.C.P., have gathered together on the Sanatorium grounds in Monrovia, Calif. for a "Home-Coming" to honor Dr. Pottenger. A special occasion this year, on September 25, was held to mark Dr. Pottenger's eightieth birthday. Dr. Pottenger was President of The American College of Physicians in 1932–33.

Separate Air Force Medical Department Established

The Technical Information Branch of the Office of the Surgeon General, Department of the Air Force, announced during the latter part of August the establishment of a separate Air Force Medical Department. Reorganization of the Office of the Surgeon General, U. S. Air Force, has been completed and will no longer be under Army control. Major General Malcolm C. Grow is the Surgeon General. Major General Harry G. Armstrong, F.A.C.P., has been named Deputy; and Brigadier General Dan C. Ogle (A.C.P. Associate), is Special Assistant to The Surgeon General.

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa., has been unanimously elected to the Advisory Board in Gastro-enterology of the American Board of Internal Medicine, succeeding Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., whose term has expired.

Dr. George E. Baker, F.A.C.P., Casper, Wyo., presided at the Rocky Mountain Medical Conference, Butte, Mont., July 31–August 1, 1949, and at the 46th Annual Meeting of the Wyoming State Medical Society at Casper, Wyo., September 12–14, 1949. Dr. Baker was President of the State Society.

Dr. Roscoe L. Pullen, F.A.C.P., Seattle, Wash., has been appointed Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice-Dean of Tulane University of Louisiana School of Medicine, New Orleans, effective October 1, 1949.

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has succeeded Dr. Hugh J. Morgan, F.A.C.P., Nashville, as a member of the American Board of Internal Medicine.

Dr. William Walter Hargrave, (MC), USN, F.A.C.P., retired from active duty in the Navy on October 1, 1949, with the rank of Commodore. His last duty assignment was that as Senior Medical Officer and Head of the Department of Hygiene at the U. S. Naval Academy, Annapolis. Dr. Hargrave is now the Health Officer for the Campbell-Charlotte Health District, Rustburg, Va.

OBITUARIES

DR. JORGE RODRIGUEZ MUNIZ

Dr. Jorge Rodriguez Muniz, F.A.C.P., Havana, Cuba, died of coronary disease May 21, 1949, at the age of 59. Dr. Muniz received his B.S. degree from the Institute of Havana in 1906. He graduated in medicine from the University of Havana School of Medicine, June 28, 1911. After his internship in Covadonga Sanitarium, he entered medical practice for some time outside of Havana. In 1926, he joined the Department of Gastro-enterology of the Mount Sinai Hospital at New York where he worked first as a student in postgraduate courses in gastro-enterology and proctology and later as Instructor and Clinical Associate in the Postgraduate School. His teacher and good friend, Dr. Asher Winkelstein, once wrote about him: "His splendid personality, his unusual intelligence and his great ability, particularly in the field of proctology, together with a sympathetic attitude towards his patients, combine to make Dr. Muniz one of the most brilliant members of our Postgraduate School." He left the United States and many good friends in the Mount Sinai group and other centers and began to practice in Havana in the field of gastro-enterology and proctology in which he had been working until his death. Shortly after his return to Havana he was appointed proctologist and gastro-enterologist at the Freyre de Andrade Municipal Hospital which he served ever since. Dr. Muniz has published many articles in Cuba and in the United States, especially in relation to ulcerative colitis and other proctologic and gastro-enterologic topics.

He was a Fellow of the American College of Physicians (1941) and a member of the Cuban Society of Clinical Studies, the Societas Internationalis Gastro-enterological, the National Gastro-enterological Association, the American Proctologic Society and the Cuban National Medical College.

In the course of years, Dr. Muniz established a very active practice in his field and in internal medicine. He always showed such an interest in the problems of his patients that he has left a great sense of loss among them. He was indeed a very fine and able physician who will always be remembered by all who knew him.

José J. Centurión, M.D., F.A.C.P.,
Governor for Cuba

DR. FRANK HARRELL REDWOOD

Frank Harrell Redwood, M.D., F.A.C.P., a native of Virginia, died on May 27, 1949. Dr. Redwood was born at Suffolk, March 22, 1891, graduated from the Medical College of Virginia in 1913, interned in the Memorial Hospital, Richmond, in 1914, and did postgraduate work at the Presbyterian Hospital and the Neurological Institute, New York City, from 1916 to 1918. Subsequently Dr. Redwood served in the Medical Reserve Corps of the U. S. Army during World War I.

Returning to Virginia, Dr. Redwood became Attending Neurologist in the Norfolk General Hospital and the Hospital of St. Vincent de Paul, and Consulting Neurologist to the Memorial, Leigh, and U. S. Marine Hospitals. He became a Fellow of the American College of Physicians in 1935. He was a Former President of the Norfolk County Medical Society and a member of the American and Southern Medical Associations, The Medical Society of Virginia, the Association for Research in Nervous and Mental Diseases and the American Psychiatric Association.

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31ST ANNUAL SESSION

AMERICAN COLLEGE OF PHYSICIANS

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BOSTON, MASS., APRIL 17–21, 1950

President (General Sessions and Morning Lectures), Reginald Fitz, M.D., Boston, Mass.

General Chairman (Clinics and Panels), Chester S. Keefer, M.D., Boston, Mass.

The staffs of the many distinguished medical schools and hospitals of the Boston area will provide an exceptionally fine program of lectures, panel discussions and hospital clinics. A large attendance is anticipated. Full details concerning hotel accommodations, etc., and the tentative program of the Session will be presented in College News Notes in the ANNALS OF INTERNAL MEDICINE during the coming months.

Autumn Schedule, 1949

REGIONAL MEETINGS

THE AMERICAN COLLEGE OF PHYSICIANS

Region	*Place of Meeting*	*Date*	*Governor*
NORTH DAKOTA	Grand Forks	September 10, 1949	Robert B. Radl, M.D., F.A.C.P.
OKLAHOMA	Oklahoma City	September 10, 1949	Wann Langston, M.D., F.A.C.P.
MONTANA & WYOMING	Great Falls	September 16, 1949	Harold W. Gregg, M.D., F.A.C.P.
WESTERN PENNSYLVANIA	Pittsburgh	September 21, 1949	Charles W. Morton, M.D., F.A.C.P.
EASTERN CANADA & NEW ENGLAND	Montreal	September 23–24, 1949	Arthur T. Henderson, M.D., F.A.C.P., et al.
WESTERN NEW YORK	Buffalo	October 1, 1949	Edward C. Reifenstein, M.D., F.A.C.P.
MISSISSIPPI	Jackson	October 8, 1949	John G. Archer, M.D., F.A.C.P.
PUERTO RICO	Santurce	October 16, 1949	Rafael Rodriguez-Molina, M.D., F.A.C.P.
ARIZONA	Phoenix	October 22, 1949	Leslie R. Kober, M.D., F.A.C.P.
MID-WEST (Ill., Iowa, Ind., Mich., Minn., Wis.)	Indianapolis	November 19, 1949	James O. Ritchey, M.D., F.A.C.P.
NEW JERSEY	Newark	November 30, 1949	George H. Lathrope, M.D., F.A.C.P.
SOUTHEASTERN (Ala., Ga., Fla., S. C., Cuba)	Birmingham	December 10, 1949	E. Dice Lineberry, M.D., F.A.C.P.

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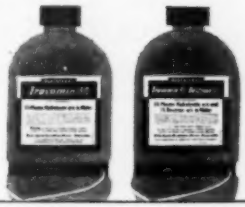

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bibliography

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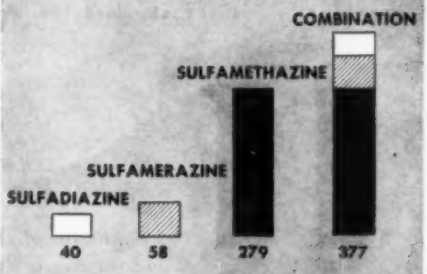

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[1] Whitby, L.: Practitioner 155: 264 (1945).

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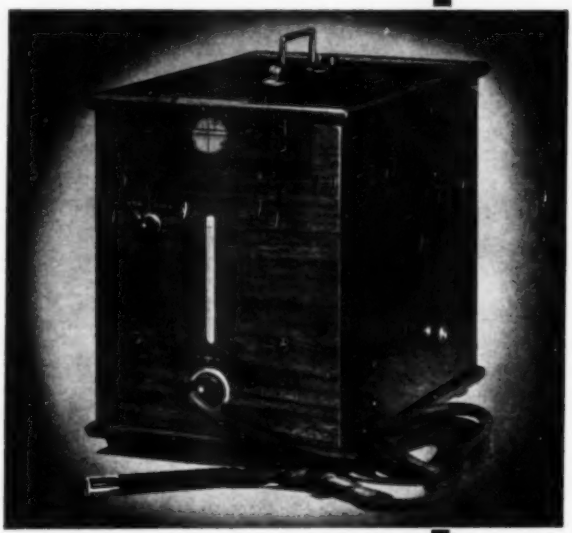

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